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(54) Title: ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO BlyS

(57) Abstract: The present invention relates to antibodies and related molecules that immunospecifically bind to BlyS. The present invention also relates to methods and compositions for detecting or diagnosing a disease or disorder associated with aberrant BlyS expression or inappropriate function of BlyS comprising antibodies or fragments or variants thereof or related molecules that immunospecifically bind to BlyS. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BlyS expression or inappropriate BlyS function comprising administering to an animal an effective amount of one or more antibodies or fragments or variants thereof or related molecules that immunospecifically bind to BlyS.



ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO BLyS

INTRODUCTION

[0001] The present invention relates to antibodies and related molecules that immunospecifically bind to BLyS. The present invention also relates to methods and compositions for detecting, diagnosing, or prognosing a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor, comprising antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS function or BLyS receptor function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS.

BACKGROUND OF THE INVENTION

[0002] B lymphocyte stimulator (BLyS) is a member of the tumor necrosis factor ("TNF") superfamily that induces both *in vivo* and *in vitro* B cell proliferation and differentiation (Moore *et al.*, Science 285: 260-263 (1999)). BLyS is distinguishable from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. BLyS expression is not detected on natural killer ("NK") cells, T cells or B cells, but is restricted to cells of myeloid origin. BLyS expression on resting monocytes is upregulated by interferon-gamma (IFN-gamma). The gene encoding BLyS has been mapped to chromosome 13q34.

[0003] BLyS is expressed as a 285 amino acid type II membrane-bound polypeptide and a soluble 152 amino acid polypeptide (Moore *et al.*, 1999 *supra*). The membrane-bound form of BLyS has a predicted transmembrane spanning domain between amino acid residues 47 and 73. The NH₂-terminus of the soluble form of BLyS begins at Ala¹³⁴

of the membrane-bound form of BLyS. Soluble recombinant BLyS has been shown to induce *in vitro* proliferation of murine splenic B cells and to bind to a cell-surface receptor on these cells (Moore *et al.*, 1999 *supra*). Soluble BLyS administration to mice has been shown to result in an increase in the proportion of CD45R^{dull}, Ly6D^{bright} (also known as ThB) B cells and an increase in serum IgM and IgA levels (Moore *et al.*, 1999 *supra*). Thus, BLyS displays a B cell tropism in both its receptor distribution and biological activity.

[0004] Levels of BLyS protein have been found to be elevated in patients with autoimmune disease, including systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren's syndrome (Zhang *et al.*, *The Journal of Immunology*, (2001) 166:6-10; Cheema *et al.*, *Arthritis and Rheumatism* (2001) 44:1313-1319; and Groom *et al.*, *Journal of Clinical Investigation* (2002) 109:59-68). Furthermore, administration of a soluble form of a BLyS receptor, TACI, has been shown to alleviate the autoimmune phenotype of NZBWF1 and MRL-*lpr/lpr* mice (Gross *et al.*, *Nature*, (2000) 404:995-999). Thus, antibodies and related molecules that immunospecifically bind to BLyS may find medical utility in, for example, the treatment of B cell disorders associated with autoimmunity. In other embodiments, antibodies and related molecules that immunospecifically bind to BLyS may find medical utility in for example, neoplasia or immunodeficiency syndromes.

SUMMARY OF THE INVENTION

[0005] The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (*e.g.*, the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on

monkey monocytes), preferably human BLYS. The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with aberrant BLYS or BLYS receptor expression or inappropriate function of BLYS or BLYS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, use of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLYS. Diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma). The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLYS or BLYS receptor expression or inappropriate function of BLYS or BLYS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, administering to said animal an effective amount of one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLYS. Diseases and disorders which can be prevented, treated or ameliorated by administering an effective amount of an antibody of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0006] Using phage display technology, the present inventors have identified single chain antibody molecules ("scFvs") that immunospecifically bind to BLYS, including scFvs that immunospecifically bind to soluble BLYS, scFvs that immunospecifically bind the membrane-bound form of BLYS, and scFvs that immunospecifically bind to both the soluble form and the membrane-bound form of BLYS. Antibodies of the present invention are defined as able to bind the membrane bound and/or soluble forms of BLYS according

to the assays described in Examples 1 through 19. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLYS, the membrane-bound form of BLYS, and/or both the soluble form and membrane-bound form of BLYS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[0007] In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 - 2128, preferably SEQ ID NOS: 834 - 872, 1570 - 1595, and 1886 - 1908, and most preferably SEQ ID NOS: 1 - 46, 321 - 329, 1563 - 1569, and 1881 - 1885, as referred to in Table 1 below. In specific embodiments, the present invention relates to scFvs that immunospecifically bind the soluble form of BLYS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1880, preferably SEQ ID NOS: 1570 - 1595, and most preferably SEQ ID NOS: 1563 - 1569, as referred to in Table 1, below. In other embodiments, the present invention also relates to scFvs that immunospecifically bind the membrane-bound form of BLYS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128, preferably SEQ ID NOS: 1886 - 1908, and most preferably SEQ ID NOS: 1881 - 1885, as referred to in Table 1 below. The present invention further relates to scFvs that immunospecifically bind both the membrane-bound form and soluble form of BLYS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562, preferably SEQ ID NOS: 834 - 872, and most preferably SEQ ID NOS: 1 - 46, and 321 - 329, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLYS, the membrane-bound form of BLYS, and/or both the soluble form and membrane-bound form of BLYS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[0008] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that

immunospecifically bind to a polypeptide or polypeptide fragment of BLYS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the variable heavy ("VH") domains referred to in Table 1, below, or any one of the variable light ("VL") domains referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. In another preferred embodiment, antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLYS, the membrane-bound form of BLYS, and/or both the soluble form and membrane-bound form of BLYS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0009] The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLYS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ

ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLYS, the membrane-bound form of BLYS, and/or both the soluble form and membrane-bound form of BLYS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0010] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLYS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one, two, three or more of the VH complementarity determining regions ("CDRs") (*i.e.*, VH CDR1, VH CDR2, or VH CDR3) referred to in Table 1 and/or any one, two, three or more of the VL CDRs (*i.e.*, VL CDR1, VL CDR2, or VL CDR3) referred to in Table 1. In one embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1 and/or any one of the VL CDR1s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1 and/or any one of the VL CDR2s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 and/or any one of the VL CDR3s referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLYS, the membrane-bound form of BLYS, and/or both the soluble form and membrane-bound form of BLYS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0011] In another embodiment, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) immunospecifically bind to a polypeptide or polypeptide fragment of BLYS, and

comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, any one of the VH CDR2s referred to in Table 1, and/or any one of the VH CDR3s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, any one of the VL CDR2s referred to in Table 1, and/or any one of the VL CDR3s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, at least one, two, three, four, five, six, or more CDRs that correspond to the same scFv referred to in Table 1, more preferably where CDR1, CDR2, and CDR3 of the VL domain correspond to the same scFv or where CDR1, CDR2, and CDR3 of the VH domain correspond to the same scFv, and most preferably where all six CDRs correspond to the same scFv referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLYS, the membrane-bound form of BLYS, and/or both the soluble form and membrane-bound form of BLYS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0012] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that: immunospecifically bind to the soluble form of BLYS (e.g., a polypeptide consisting of amino acids 134 - 285 of SEQ ID NO:3228); that immunospecifically bind to the membrane-bound form of BLYS (e.g., a polypeptide consisting of amino acids 1 - 285 of SEQ ID NO:3228 or a BLYS polypeptide expressed on the surface of monocytes) and/or that immunospecifically bind to both the soluble form and membrane-bound form of BLYS. In a preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form of BLYS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the soluble form of BLYS. In another preferred embodiment, antibodies of the present invention immunospecifically bind to the membrane-bound form of BLYS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL

CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the membrane-bound form of BLyS. In yet another preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form and membrane-bound form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically binds to the soluble form and membrane-bound form of BLyS. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a VH domain and a VL domain corresponding to the same scFv disclosed in Table 1, which antibodies immunospecifically bind to the soluble form of BLyS, the membrane-bound form of BLyS, or both the soluble form and membrane-bound form of BLyS. Nucleic acid molecules encoding these antibodies are also encompassed by the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0013] The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to both BLyS and APRIL (preferably to the soluble forms of each of these molecules), said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind to both BLyS and APRIL, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:3240-3247 as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:3240-3247, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind to both BLyS and APRIL comprise, or alternatively consist

of, the VH and VL domain from a single scFv of SEQ ID NOS: SEQ ID NOS:3240-3247, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind both BLyS and APRIL, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0014] The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a heterotrimeric protein comprising at least one BLyS polypeptide (preferably amino acids 134-285 of SEQ ID NO:3228), said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention that immunospecifically bind heterotrimeric protein comprising at least one BLyS polypeptide, comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind heterotrimeric protein comprising at least one BLyS polypeptide, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:3240-3247 as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:3240-3247, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention that immunospecifically bind heterotrimeric protein comprising at least one BLyS polypeptide, comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ ID NOS:3240-3247, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind a heterotrimeric protein comprising at least one BLyS polypeptide, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[0015] A VH domain of an amino acid sequence disclosed herein may be combined with a VL domain of an amino acid sequence disclosed herein, or other VL domains, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a

VL domain of an amino acid sequence disclosed herein may be combined with a VH domain of an amino acid sequence disclosed herein, or other VH domains. Further, one or more CDRs disclosed herein may be taken from a VH or VL domain and incorporated into a suitable framework as discussed *infra*.

[0016] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (including derivatives)) comprising, or alternatively consisting of, of VH domains, VL domains and/or CDRs described herein, which antibodies, immunospecifically bind to BLYS (e.g., soluble BLYS and membrane-bound BLYS) and can be routinely assayed for immunospecific binding to BLYS using methods known in the art, such as, for example, the immunoassays disclosed *infra*. Antibodies and antibody fragments or variants (including derivatives) of the invention may include, for example, one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue). These alterations may be made in one or more framework regions and/or one or more CDR's. The antibodies of the invention (including antibody fragments, and variants and derivative thereof) can be routinely made by methods known in the art. Molecules comprising, or alternatively consisting of, fragments or variants of any of the VH domains, VH CDRs, VL domains, and VL CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention. Nucleic acid molecules encoding these antibodies and molecules (including fragments, variants, and derivatives) are also encompassed by the invention.

[0017] The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs)). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including

molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

[0018] The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention.

[0019] The present invention also provides for a nucleic acid molecule, generally isolated, encoding an antibody (including molecules such as scFvs, which comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

[0020] The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant BLYS or BLYS receptor expression or inappropriate BLYS or BLYS receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLYS. Diseases and disorders which can

be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0021] In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (*e.g.*, AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (*e.g.*, an immunodeficiency).

[0022] The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLYS or BLYS receptor expression or inappropriate BLYS or BLYS receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLYS. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0023] In specific embodiments, the present invention encompasses methods and compositions (*e.g.*, antagonistic anti-BLYS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypergammaglobulinemia (*e.g.*, AIDS, autoimmune diseases, and some immunodeficiency syndromes). In other specific embodiments, the present invention encompasses methods and compositions (*e.g.*, agonistic anti-BLYS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypogammaglobulinemia (*e.g.*, an immunodeficiency syndrome).

[0024] Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders).

[0025] Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable

immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia, lymphoplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome, combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

DEFINITIONS

[0026] The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody fragments as well as variants (including derivatives) of antibodies and antibody fragments. Examples of molecules which are described by the term "antibody" in this application include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab' fragments, F(ab')₂, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a VL or a VH domain. The term "single chain Fv" or "scFv" as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that immunospecifically bind to BLyS may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to BLyS do not cross-react with other antigens. Antibodies that immunospecifically bind to BLyS can be identified, for example, by immunoassays or other techniques known to those of skill in the art, *e.g.*, the immunoassays described in the Examples below.

[0027] Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, antiidiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to

antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ and IgA₂) or subclass of immunoglobulin molecule.

[0028] Antibodies of the invention may also include multimeric forms of antibodies. For example, antibodies of the invention may take the form of antibody dimers, trimers, or higher-order multimers of monomeric immunoglobulin molecules. Dimers of whole immunoglobulin molecules or of F(ab')₂ fragments are tetravalent, whereas dimers of Fab fragments or scFv molecules are bivalent. Individual monomers within an antibody multimer may be identical or different, *i.e.*, they may be heteromeric or homomeric antibody multimers. For example, individual antibodies within a multimer may have the same or different binding specificities. Multimerization of antibodies may be accomplished through natural aggregation of antibodies or through chemical or recombinant linking techniques known in the art. For example, some percentage of purified antibody preparations (*e.g.*, purified IgG1 molecules) spontaneously form protein aggregates containing antibody homodimers, and other higher-order antibody multimers. Alternatively, antibody homodimers may be formed through chemical linkage techniques known in the art. For example, heterobifunctional crosslinking agents including, but not limited to, SMCC [succinimidyl 4-(maleimidomethyl)cyclohexane-1-carboxylate] and SATA [*N*-succinimidyl *S*-acetylthio-acetate] (available, for example, from Pierce Biotechnology, Inc. (Rockford, IL)) can be used to form antibody multimers. An exemplary protocol for the formation of antibody homodimers is given in Ghetie *et al.*, *Proceedings of the National Academy of Sciences USA* (1997) 94:7509-7514, which is hereby incorporated by reference in its entirety. Antibody homodimers can be converted to Fab'2 homodimers through digestion with pepsin. Another way to form antibody homodimers is through the use of the autophilic T15 peptide described in Zhao and Kohler, *The Journal of Immunology* (2002) 25:396-404, which is hereby incorporated by reference in its entirety.

[0029] Alternatively, antibodies can be made to multimerize through recombinant DNA techniques. IgM and IgA naturally form antibody multimers through the interaction with the J chain polypeptide. Non-IgA or non-IgM molecules, such as IgG molecules, can be engineered to contain the J chain interaction domain of IgA or IgM, thereby conferring

the ability to form higher order multimers on the non-IgA or non-IgM molecules. (see, for example, Chintalacharuvu et al., (2001) *Clinical Immunology* 101:21-31. and Frigerio et al., (2000) *Plant Physiology* 123:1483-94., both of which are hereby incorporated by reference in their entireties.) ScFv dimers can also be formed through recombinant techniques known in the art; an example of the construction of scFv dimers is given in Goel et al., (2000) *Cancer Research* 60:6964-6971 which is hereby incorporated by reference in its entirety. Antibody multimers may be purified using any suitable method known in the art, including, but not limited to, size exclusion chromatography.

[0030] Unless otherwise defined in the specification, specific binding or immunospecific binding by an anti-BLyS antibody means that the anti-BLyS antibody binds BLyS but does not significantly bind to (i.e., cross react with) proteins other than BLyS, such as other proteins in the same family of proteins, e.g., other TNF family ligands). An antibody that binds BLyS protein and does not cross-react with other proteins is not necessarily an antibody that does not bind said other proteins in all conditions; rather, the BLyS -specific antibody of the invention preferentially binds BLyS compared to its ability to bind said other proteins such that it will be suitable for use in at least one type of assay or treatment, i.e., give low background levels or result in no unreasonable adverse effects in treatment. It is well known that the portion of a protein bound by an antibody is known as the epitope. An epitope may either be linear (i.e., comprised of sequential amino acids residues in a protein sequences) or conformational (i.e., comprised of one or more amino acid residues that are not contiguous in the primary structure of the protein but that are brought together by the secondary, tertiary or quaternary structure of a protein). Given that BLyS -specific antibodies bind to epitopes of BLyS, an antibody that specifically binds BLyS may or may not bind fragments of BLyS and/or variants of BLyS (e.g., proteins that are at least 90% identical to BLyS) depending on the presence or absence of the epitope bound by a given BLyS-specific antibody in the BLyS fragment or variant. Likewise, BLyS-specific antibodies of the invention may bind species orthologues of BLyS (including fragments thereof) depending on the presence or absence of the epitope recognized by the antibody in the orthologue. Additionally, BLyS-specific antibodies of the invention may bind modified forms of BLyS, for example, BLyS fusion proteins. In such a case when antibodies of the invention bind BLyS fusion proteins, the antibody must make binding contact with the BLyS moiety

of the fusion protein in order for the binding to be specific. Antibodies that specifically bind to BLYS can be identified, for example, by immunoassays or other techniques known to those of skill in the art, *e.g.*, the immunoassays described in the Examples below.

[0031] Furthermore, in the present application certain antibodies may be specific for either the membrane bound form of BLYS, or the soluble form of BLYS (*i.e.*, 134-285 of SEQ ID NO:2, preferably trimers of proteins consisting of amino acids 134-285 of SEQ ID NO:2), or both. Antibodies of the present invention are defined as able to bind the membrane bound and/or soluble forms of BLYS according to the assays described in Examples 1 through 19.

[0032] Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table 1, or a fragment or variant thereof.

[0033] An antibody of the invention "which binds the soluble form of BLYS" is one which binds the 152 amino acid soluble form of the BLYS protein (amino acids 134- 285 of SEQ ID NO:3228). In specific embodiments of the invention, an antibody of the invention "which binds the soluble form of BLYS" does not also bind the membrane-bound or membrane-associated form of BLYS. Assays which measure binding to the soluble form of BLYS include, but are not limited to, receptor binding inhibition assay or capture of soluble BLYS from solution as described in Examples 8 and 9.

[0034] An antibody of the invention "which binds the membrane-bound form of BLYS" is one which binds the membrane-associated (uncleaved) BLYS protein. In specific embodiments of the invention, an antibody of the invention "which binds the membrane-bound form of BLYS" does not also bind the soluble form of BLYS. Binding to HIS-tagged BLYS (as described herein) in an ELISA is an indicator that an antibody binds the membrane-bound form of BLYS, but should not be relied upon as proof of specificity for the membrane-bound form of BLYS. Assays that may be relied upon as proof of an antibody's specificity for membrane-bound BLYS, include, but are not limited to, binding to plasma membranes expressing BLYS as described in Example 2. An antibody of the invention "which binds the both the soluble form and the membrane-bound form of BLYS" is one which binds both the membrane-bound form and the soluble form of BLYS.

[0035] The term "variant" as used herein refers to a polypeptide that possesses a similar or identical function as a BLYS polypeptide, a fragment of BLYS, an anti-BLYS

antibody or antibody fragment thereof, but does not necessarily comprise a similar or identical amino acid sequence of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof, or possess a similar or identical structure of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof. A variant having a similar amino acid refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide comprising, or alternatively consisting of, an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to a nucleotide sequence encoding a BLyS polypeptide (e.g., SEQ ID NO:3228), a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein. A polypeptide with similar structure to a BLyS polypeptide, a fragment of BLyS, an anti-BLyS antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a BLyS polypeptide, a fragment of BLyS, an

anti-BLyS antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can be determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

[0036] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical overlapping positions/total number of positions x 100%). In one embodiment, the two sequences are the same length.

[0037] The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268(1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877(1993). The BLASTn and BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403-410(1990) have incorporated such an algorithm. BLAST nucleotide searches can be performed with the BLASTn program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3389-3402(1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (*e.g.*, BLASTx and BLASTn) can be used. (*See* <http://www.ncbi.nlm.nih.gov>.)

[0038] Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other algorithms for sequence analysis known in the art include ADVANCE and ADAM as described in Torellis and Robotti *Comput. Appl. Biosci.*, 10 :3-5(1994); and FASTA described in Pearson and Lipman *Proc. Natl. Acad. Sci.* 85:2444-8(1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

[0039] The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino acid sequence of a BLYS polypeptide, a fragment of BLYS, or an antibody of the invention that immunospecifically binds to BLYS, which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a BLYS polypeptide, a fragment of BLYS, an antibody that immunospecifically binds to BLYS which has been modified, *e.g.*, by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a BLYS polypeptide, a fragment of BLYS, or an anti-BLYS antibody, may be modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a BLYS polypeptide, a fragment of BLYS, or an anti-BLYS antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a BLYS polypeptide, a fragment of BLYS, or an anti-BLYS antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a BLYS polypeptide, a fragment of BLYS, or an anti-BLYS antibody, described herein.

[0040] The term "epitopes" as used herein refers to portions of BLYS having antigenic or immunogenic activity in an animal, preferably a mammal. An epitope having immunogenic activity is a portion of BLYS that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of BLYS to which an antibody immunospecifically binds as determined by any method known in the art, for example, by

the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic.

[0041] The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, at least 150 amino acid residues, at least 175 amino acid residues, at least 200 amino acid residues, or at least 250 amino acid residues, of the amino acid sequence of BLyS, or an anti-BLyS antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically binds to BLyS.

[0042] The term "fusion protein" as used herein refers to a polypeptide that comprises, or alternatively consists of, an amino acid sequence of an anti-BLyS antibody of the invention and an amino acid sequence of a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain).

[0043] The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0044] By "isolated antibody" is intended an antibody removed from its native environment. Thus, an antibody produced and/or contained within a recombinant host cell is considered isolated for purposes of the present invention.

DESCRIPTION OF THE FIGURES

[0045] Figure 1. ELISA results for three scFvs, I006E07, I008D05 and I016F04, that immunospecifically bind to U937 membranes, but not to bind to or cross-react with TNF-alpha or BSA.

[0046] Figure 2. The results for three scFvs, I016H07, I001C09 and I018D07, in a receptor inhibition assay.

[0047] Figure 3. ELISA results for two scFvs (I022D01 and I031F02) demonstrating their ability to bind to human BLyS and to cross-react with mouse BLyS, but not to bind to or cross-react with other antigens of the TNF ligand family.

[0048] Figure 4. ELISA results for three scFvs (I031F09, I050A12, and I051C04) binding to U937 plasma membranes when either BLyS or TNF-alpha is used as a competitor.

[0049] Figure 5. Kinetic analysis of scFv antibody I003C02. A dilution series of I003C02 from 3nM to 825nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

[0050] Figure 6. Typical titration curves for two scFv antibodies (I007F11 and I050A07) are shown in Figure 6. Unlabelled BLyS competed for binding to its receptor with an IC_{50} value of 0.8 nM. The IC_{50} values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

[0051] Figure 7. ELISA results for three scFvs clones (I074B12, I075F12 and I075A02) that immunospecifically bind to immobilized BLyS, but not to U937 plasma membranes, TNF-alpha or BSA. As a control, a phage antibody that recognizes TNF α , is also shown in Figure 7.

[0052] Figure 8. The results for two scFvs (I025B09 and I026C04) in a receptor inhibition assay.

[0053] Figure 9. ELISA results for two scFvs clones (I067F05 and I078D02) demonstrating their ability to bind to immobilized human BLyS and to cross-react with immobilized mouse BLyS, but not to bind to or cross-react with other antigens of the TNF ligand family.

[0054] As a control, a phage antibody that recognizes TNF α , is also shown in Figure 7.

[0055] Figure 10. Kinetic analysis of scFV antibody I002A01. A dilution series of I002A01 from 3nM to 1650nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

[0056] Figure 11. Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in Figure 11. Unlabelled BLYS competed for binding to its receptor with an inhibitory constant 50 (IC_{50}) value of 0.66 nM. The IC_{50} values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

[0057] Figure 12. ELISA results for three clones (I079C01, I081C10 and I082A02) demonstrating their ability to bind histidine-tagged BLYS, U937 plasma membranes, but not to bind immobilized biotinylated BLYS.

[0058] Figure 13. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to U937 plasma membranes when either histidine-tagged BLYS or biotinylated BLYS is used as a competitor.

[0059] Figure 14. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in Figure 14. An anti-TNF α antibody that does not recognize BLYS was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

[0060] Figure 15. A typical example of the binding curves generated for the scFv antibody I082C03 is shown in Figure 15. The off-rate for this clone was calculated as $2 \times 10^{-3} \text{ s}^{-1}$. The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv.

[0061] Figure 16. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to P388 plasma membranes when either histidine-tagged BLYS or biotinylated BLYS is used as a competitor.

DETAILED DESCRIPTION OF THE INVENTION

[0062] The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLYS or a fragment or variant of BLYS. In particular, the invention provides antibodies such as, for example, single chain Fvs (scFvs) having an

amino acid sequence of any one of SEQ ID NOS:1 - 2128, as referred to in Table 1. In particular, the present invention encompasses antibodies that immunospecifically bind to a polypeptide, a polypeptide fragment or variant, or an epitope of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (*e.g.*, the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes) (as determined by immunoassays known in the art for assaying specific antibody-antigen binding).

[0063] The polypeptide sequence shown in SEQ ID NO:3228 was obtained by sequencing and translating the cDNA of the HNEDU15 clone which was deposited on October 22, 1996 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, and assigned ATCC Accession No. 97768. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0064] The polypeptide sequence shown in SEQ ID NO:3229 was obtained by sequencing and translating the cDNA of the HDPMC52 clone, which was deposited on December 10, 1998 at the American Type Culture Collection, and assigned ATCC Accession No. 203518. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, CA). The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0065] The BLyS polypeptides bound by the antibodies of the invention may be in monomers or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to antibodies that bind monomers and multimers of the BLyS polypeptides of the invention, their preparation, and compositions (preferably, pharmaceutical compositions) containing them. In specific embodiments, the antibodies of the invention bind BLyS monomers, dimers, trimers or tetramers. In additional embodiments, the antibodies of the invention bind at least dimers, at least

trimers, or at least tetramers of BLYS.

[0066] Multimeric BLYS bound by the antibodies of the invention may be homomers or heteromers. A BLYS homomer, refers to a multimer containing only BLYS polypeptides (including BLYS fragments, variants, and fusion proteins, as described herein). These homomers may contain BLYS polypeptides having identical or different amino acid sequences. In specific embodiments, the antibodies of the invention bind a BLYS homodimer (e.g., containing two BLYS polypeptides having identical or different amino acid sequences) or a BLYS homotrimer (e.g., containing three BLYS polypeptides having identical or different amino acid sequences). In a preferred embodiment, the antibodies of the invention bind homotrimers of BLYS. In additional embodiments, the antibodies of the invention bind a homomeric BLYS multimer which is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0067] Heteromeric BLYS refers to a multimer containing heterologous polypeptides (i.e., polypeptides of a different protein) in addition to the BLYS polypeptides of the invention. In a specific embodiment, the antibodies of the invention bind a BLYS heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind a heteromeric BLYS multimer which is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer. In highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising both BLYS polypeptides and APRIL polypeptides (SEQ ID NO:3239; GenBank Accession No. AF046888; PCT International Publication Number WO97/33902; J. Exp. Med. 188(6):1185-1190) or fragments or variants thereof. In other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising one BLYS polypeptide (including fragments or variants) and two APRIL polypeptides (including fragments or variants). In still other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising two BLYS polypeptides (including fragments or variants) and one APRIL polypeptide (including fragments or variants). In a further nonexclusive embodiment, the heteromers bound by the antibodies of the invention contain CD40 ligand polypeptide sequence(s), or biologically active fragment(s) or variant(s) thereof.

[0068] In particularly preferred embodiments, the antibodies of the invention bind homomeric, especially homotrimeric, BLYS polypeptides, wherein the individual protein

components of the multimers consist of the mature form of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof. In other specific embodiments, antibodies of the invention bind heteromeric, especially heterotrimeric, BLyS polypeptides such as a heterotrimer containing two BLyS polypeptides and one APRIL polypeptide or a heterotrimer containing one BLyS polypeptide and two APRIL polypeptides, and wherein the individual protein components of the BLyS heteromer consist of the mature extracellular soluble portion of either BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof, or the mature extracellular soluble portion APRIL (e.g., amino acid residues 105-250 of SEQ ID NO:3239) or fragments or variants thereof.

[0069] In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLyS monomeric protein. In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLyS multimeric, especially trimeric, protein. In other embodiments, antibodies of the invention bind conformational epitopes that arise from the juxtaposition of BLyS with a heterologous polypeptide, such as might be present when BLyS forms heterotrimers (e.g., with APRIL polypeptides (e.g., SEQ ID NO:3239)), or in fusion proteins between BLyS and a heterologous polypeptide.

[0070] In a specific embodiment, antibodies of the invention that specifically bind heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide, comprise all or a portion of SEQ ID NOS: 1881 or 1884 (e.g., one or more CDR regions, a VH domain or a VL domain). In a specific embodiment, the heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide comprise two BLyS polypeptides and one APRIL polypeptide. In a specific embodiment, the heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide comprise one BLyS polypeptide and two APRIL polypeptides.

[0071] In a specific embodiment, antibodies of the invention that specifically bind heterotrimers containing at least one BLyS polypeptide and at least one APRIL polypeptide, comprise all or a portion of any one of SEQ ID NOS: 3240-3247 (e.g., one or more CDR regions, a VH domain or a VL domain). The sequences of SEQ ID NOS: 3240-3247 are presented after Table 1 just prior to the claims. In a specific embodiment, the heterotrimers containing at least one BLyS polypeptide and at least one APRIL

polypeptide comprise two BLYS polypeptides and one APRIL polypeptide. In a specific embodiment, the heterotrimers containing at least one BLYS polypeptide and at least one APRIL polypeptide comprise one BLYS polypeptide and two APRIL polypeptides.

[0072] BLYS multimers bound by the antibodies of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, BLYS multimers, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, BLYS heteromultimers, such as, for example, BLYS heterotrimers or BLYS heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, BLYS multimers are formed by covalent associations with and/or between the BLYS polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:3228 or SEQ ID NO:3229). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a BLYS fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a BLYS-Fc fusion protein. In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from CD40L, or a soluble fragment thereof. In another embodiment, two or BLYS polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers).

Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple BLYS polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0073] In one embodiment, antibodies of the invention immunospecifically bind a BLYS polypeptide having the amino acid sequence of SEQ ID NO:3228 or as encoded by the cDNA clone contained in ATCC No. 97768, or a polypeptide comprising a portion (i.e., a fragment) of the above polypeptides. In another embodiment, the invention provides an antibody that binds an isolated BLYS polypeptide having the amino acid sequence of SEQ ID NO:3229 or the amino acid sequence encoded by the cDNA clone contained in ATCC No. 203518, or an antibody that binds polypeptide comprising a portion (i.e., fragment) of the above polypeptides.

[0074] Antibodies of the invention that bind BLYS polypeptides may bind them in as isolated polypeptides, in their naturally occurring state and/or their native conformation. By "isolated polypeptide" is intended a polypeptide removed from its native environment. Thus, a polypeptide produced by and/or contained within a recombinant host cell is considered isolated for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host cell. Thus, antibodies of the present invention may bind recombinantly produced BLYS polypeptides.

[0075] Antibodies of the present invention may also bind BLYS expressed on the surface of a cell, wherein said BLYS polypeptide is encoded by a polynucleotide encoding amino acids 1 to 285 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide. In certain embodiments, said BLYS polypeptide expressed on the surface of a cell is a recombinant BLYS polypeptide. In other embodiments, said BLYS polypeptide expressed on the surface of the cell is a naturally occurring BLYS polypeptide. As a non-limiting example, an antibody of the invention may bind a BLYS expressed on the surface of the cell wherein Lys-132 and/or Arg-133 of the BLYS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, thereby preventing or diminishing release of the soluble form of BLYS from cells expressing BLYS.

[0076] Antibodies of the present invention may also bind BLYS secreted by a cell, wherein said BLYS polypeptide is encoded by a polynucleotide encoding amino acids 1 to

285 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide. In certain embodiments, said BLyS polypeptide secreted by a cell is a recombinant BLyS polypeptide. In other embodiments, said BLyS polypeptide secreted by a cell is a naturally occurring BLyS polypeptide.

[0077] Antibodies of the present invention immunospecifically bind to polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[0078] Additionally, antibodies of the present invention bind polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[0079] In addition, antibodies of the invention bind polypeptides or polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NOS: 3230 through 3237.

[0080] In specific embodiments, the antibodies of the present invention immunospecifically bind polypeptide fragments including polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:3228, encoded by the cDNA contained in the deposited clone, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably

as a single continuous region. Representative examples of polypeptide fragments that may be bound by the antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 285 of SEQ ID NO:3228. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length.

[0081] In specific embodiments, antibodies of the present invention bind polypeptide fragments comprising, or alternatively consisting of, amino acid residues: 1-46, 31-44, 47-72, 73-285, 73-83, 94-102, 148-152, 166-181, 185-209, 210-221, 226-237, 244-249, 253-265, and/or 277-285 of SEQ ID NO:3228. In a specific embodiment, antibodies of the invention bind an epitope comprising amino acids 165-171 of SEQ ID NO:3228. In another embodiment, the CDRs of antibodies of the invention make contacts with one or more amino acids in the the sequence of amino acids 165-171 of SEQ ID NO:3228. In another embodiment, antibodies of the invention whose CDRs make contact with one or more amino acids in the the sequence of amino acids 165-171 of SEQ ID NO:3228 disrupt BLYS- BLYS receptor interactions.

[0082] It will be recognized by one of ordinary skill in the art that mutations targeted to regions of a BLYS polypeptide of SEQ ID NO:3228 which encompass the nineteen amino acid residue insertion which is not found in the BLYS polypeptide sequence of SEQ ID NO:3229 (i.e., amino acid residues Val-142 through Lys-160 of the sequence of SEQ ID NO:3229) may affect the observed biological activities of the BLYS polypeptide. More specifically, a partial, non-limiting and non-exclusive list of such residues of the BLYS polypeptide sequence which may be targeted for mutation includes the following amino acid residues of the BLYS polypeptide sequence as shown in SEQ ID NO:3228: V-142; T-143; Q-144; D-145; C-146; L-147; Q-148; L-149; I-150; A-151; D-152; S-153; E-154; T-155; P-156; T-157; I-158; Q-159; and K-160. Thus, in specific embodiments, antibodies of the present invention that bind BLYS polypeptides which have one or more mutations in the region from V-142 through K-160 of SEQ ID NO:3228 are contemplated.

[0083] Polypeptide fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or

alternatively, consist of from about amino acid residues: 1 to 15, 16-30, 31-46, 47-55, 56-72, 73-104, 105-163, 163-188, 186-210 and 210-284 of the amino acid sequence disclosed in SEQ ID NO:3228. Additional representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 143, 1-150, 47-143, 47-150, 73-143, 73-150, 100-150, 140-145, 142-148, 140-150, 140-200, 140-225, and 140-266 of the amino acid sequence disclosed in SEQ ID NO:3229. Moreover, polypeptide fragments that may be bound by antibodies of the present invention, can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini.

[0084] Additional preferred embodiments encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (e.g., amino acid residues 1-46 of SEQ ID NO:3228), the predicted transmembrane domain of BLyS (e.g., amino acid residues 47-72 of SEQ ID NO:3228), the predicted extracellular domain of BLyS (e.g., amino acid residues 73-285 of SEQ ID NO:3228), the mature soluble extracellular domain of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228), the predicted TNF conserved domain of BLyS (e.g., amino acids 191 to 284 of SEQ ID NO:3228), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-285 of SEQ ID NO:3228).

[0085] Further additional preferred embodiments encompass polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (amino acid residues 1-46 of SEQ ID NO:3229), the predicted transmembrane domain of BLyS (amino acid residues 47-72 of SEQ ID NO:3229), the predicted extracellular domain of BLyS (amino acid residues 73-266 of SEQ ID NO:3229), the predicted TNF conserved domain of BLyS (amino acids 172 to 265 of SEQ ID NO:3229), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-266 of SEQ ID NO:3229).

[0086] Certain additional embodiments of the invention encompass antibodies that

bind polypeptide fragments comprising, or alternatively consisting of, the predicted beta-pleated sheet regions of the BLYS polypeptides of SEQ ID NO:3228 and SEQ ID NO:3229. These polypeptide fragments comprising the beta-pleated sheets of BLYS comprise, or alternatively consist of, amino acid residues Gln-144 to Ala-151, Phe-172 to Lys-173, Ala-177 to Glu-179, Asn-183 to Ile-185, Gly-191 to Lys-204, His-210 to Val-219, Leu-226 to Pro-237, Asn-242 to Ala-251, Gly-256 to Ile-263 and/or Val-276 to Leu-284 of SEQ ID NO:3228. In another, nonexclusive embodiment, these polypeptide fragments comprising the beta-pleated sheets of BLYS comprise, or alternatively consist of, amino acid residues Phe-153 to Lys-154, Ala-158 to Glu-160, Asn-164 to Ile-166, Gly-172 to Lys-185, His-191 to Val-200, Leu-207 to Pro-218, Asn-223 to Ala-232, Gly-237 to Ile-244 and/or Val-257 to Leu-265 of SEQ ID NO:3229.

[0087] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences of the invention includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228. Other combinations of amino acids sequences that may be bound by the antibodies of the invention may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] fused to [Val-142 to Lys-160] of (SEQ ID NO:3228). Other combinations of amino acids sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228 fused to a FLAG tag ; or [Met-1 to Lys-113] of SEQ ID NO:3228 fused to [Leu-114 to Thr-141] of SEQ ID NO:3228 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Val-142 to Lys-160] of SEQ ID NO:3228 fused to [Gly-161 to Gln-198] of SEQ ID NO:3228 fused to [Val-199 to Ala-248] of SEQ ID

NO:3228 fused to [Gly-249 to Leu-285] of SEQ ID NO:3228).

[0088] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; [Met-1 to Lys-113] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229. Other of amino acids sequences that may be bound by the antibodies of the invention combinations may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] fused to [Gly-142 to Gln-179] of SEQ ID NO:3229). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229 fused to a FLAG tag (SEQ ID NO:3238) or, [Met-1 to Lys-113] of SEQ ID NO:3229 fused to [Leu-114 to Thr-141] of SEQ ID NO:3229 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Gly-142 to Gln-179] of SEQ ID NO:3229 fused to [Val-180 to Ala-229] of SEQ ID NO:3229 fused to [Gly-230 to Leu-266] of SEQ ID NO:3229.

[0089] Additional embodiments of the invention encompass antibodies that bind BLYS polypeptide fragments comprising, or alternatively consisting of, functional regions of polypeptides of the invention, such as the Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index set out in Tables 9 and 10 and as described herein. In a preferred embodiment, the polypeptide fragments bound by the antibodies of the invention are antigenic (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of a complete (i.e., full-length) BLYS

polypeptide (e.g., SEQ ID NOS:3228 and 3229).

[0090] The data representing the structural or functional attributes of the BLYS polypeptide of SEQ ID NO:3228 (Table 9) or the BLYS polypeptide of SEQ ID NO:3229 (Table 10), as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier Robson analysis of beta sheet regions; Column IV represents the results of a Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schultz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

[0091] In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables 9 and 10 can be used to determine regions of the BLYS polypeptide of SEQ ID NO:3228 (Table 9) or the BLYS polypeptide of SEQ ID NO:3229 (Table 10) which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0092] The above-mentioned preferred regions set out in Tables 9 and 10 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Tables 9 and 10, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming

regions. Preferably, antibodies of the present invention bind BLyS polypeptides or BLyS polypeptide fragments and variants comprising regions of BLyS that combine several structural features, such as several (e.g., 1, 2, 3 , or 4) of the same or different region features set out above and in Tables 9 and 10.

Table 9

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	T	T	.	1.09	-1.80	.	*	F	3.06	2.72
Asp	44	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	-2.00	1.23	.	.	.	-0.60	0.19

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	T	.	-0.50	0.16	.	*	.	0.10	0.55
Gln	73	A	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	0.66	-0.46	.	.	F	0.60	1.01

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	-0.80	0.49	.	.	.	-0.60	0.38
Thr	109	A	A	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	C	0.34	-0.00	.	.	F	2.20	1.47
Ala	119	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	C	1.66	-0.60	*	.	F	1.49	0.89
Gln	136	C	1.66	-0.60	*	.	F	1.83	0.79
Gly	137	T	C	1.30	-0.60	*	.	F	2.52	1.35
Pro	138	T	C	0.33	-0.61	*	.	F	2.86	2.63
Glu	139	T	T	.	0.61	-0.61	*	.	F	3.40	1.13
Glu	140	A	T	.	1.47	-0.53	*	.	F	2.66	1.64
Thr	141	A	1.47	-0.56	.	.	F	2.12	1.84
Val	142	A	1.14	-0.99	.	.	F	1.78	1.77
Thr	143	A	T	.	0.54	-0.41	.	.	F	1.19	0.55
Gln	144	A	T	.	0.54	0.27	*	.	F	0.25	0.31
Asp	145	A	T	.	-0.27	0.19	*	.	F	0.25	0.73
Cys	146	A	T	.	-0.84	0.23	*	.	.	0.10	0.42
Leu	147	A	A	-0.58	0.43	*	.	.	-0.60	0.17
Gln	148	A	A	-0.27	0.53	*	.	.	-0.60	0.10
Leu	149	A	A	-0.57	0.53	*	*	.	-0.30	0.32
Ile	150	A	A	-0.57	0.34	*	.	.	0.30	0.52

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	151	.	A	C	-0.21	-0.34	.	*	.	1.40	0.52
Asp	152	T	T	.	0.39	-0.26	.	*	F	2.45	0.91
Ser	153	T	C	0.08	-0.51	.	.	F	3.00	2.00
Glu	154	T	C	-0.00	-0.71	.	.	F	2.70	2.86
Thr	155	T	C	0.89	-0.53	*	.	F	2.40	1.20
Pro	156	.	.	.	B	.	.	C	1.52	-0.13	*	.	F	1.56	1.55
Thr	157	.	.	.	B	T	.	.	1.18	-0.51	*	.	F	1.92	1.79
Ile	158	A	.	.	B	.	.	.	1.18	-0.09	.	.	F	1.08	1.23
Gln	159	T	T	.	0.93	-0.19	.	.	F	2.04	1.07
Lys	160	T	T	.	0.93	0.14	*	.	F	1.60	1.16
Gly	161	T	T	.	0.44	0.14	*	.	F	1.44	2.38
Ser	162	T	T	.	-0.10	0.24	*	.	F	1.28	1.19
Tyr	163	.	.	.	B	T	.	.	0.58	0.49	*	.	.	0.12	0.44
Thr	164	.	.	B	B	.	.	.	0.29	0.91	*	.	.	-0.44	0.69
Phe	165	.	.	B	B	.	.	.	-0.57	1.40	*	.	.	-0.60	0.54
Val	166	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	167	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	168	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	169	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu	170	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ter	171	A	0.19	0.46	*	.	.	0.20	0.71
Phe	172	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	173	T	.	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	174	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	175	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	176	A	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	177	A	A	1.66	-1.00	*	.	F	1.35	0.76
Leu	178	A	A	1.61	-1.00	.	.	F	1.20	1.54
Glu	179	A	A	1.50	-1.43	.	.	F	0.90	1.98
Glu	180	A	A	1.89	-1.41	*	.	F	0.90	3.16
Lys	181	A	A	1.30	-1.91	*	.	F	0.90	7.66
Glu	182	A	A	1.08	-1.91	.	.	F	0.90	3.10
Asn	183	A	A	1.03	-1.23	*	*	F	0.90	1.48
Lys	184	A	A	1.08	-0.59	*	.	F	0.75	0.55
Ile	185	A	A	1.08	-0.59	*	*	.	0.60	0.63
Leu	186	A	A	0.72	-0.59	*	*	.	0.60	-0.68
Val	187	A	A	0.38	-0.50	.	*	.	0.30	0.49
Lys	188	A	A	0.13	-0.07	*	*	F	0.45	0.69
Glu	189	A	T	.	-0.61	0.00	*	*	F	0.40	1.32
Thr	190	T	T	.	-0.42	0.10	.	*	F	0.80	1.54
Gly	191	T	T	.	-0.50	0.24	*	.	F	0.65	0.67
Tyr	192	T	T	.	0.11	0.93	*	*	.	0.20	0.27
Phe	193	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.60	0.29
Phe	194	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.60	0.29
Ile	195	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	196	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	197	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	198	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	199	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	200	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92

Table 9 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Tyr 201	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr 202	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp 203	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys 204	A	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr 205	A	A	0.90	-0.16	.	.	F	0.60	1.73
Tyr 206	A	A	1.11	-0.21	.	.	.	0.45	1.03
Ala 207	A	A	0.61	0.29	.	.	.	-0.30	0.70
Met 208	A	A	-0.28	0.97	.	.	.	-0.60	0.40
Gly 209	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His 210	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu 211	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile 212	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln 213	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg 214	A	A	.	B	.	.	.	1.08	-0.59	.	*	F	0.90	1.62
Lys 215	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys 216	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val 217	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His 218	.	A	B	B	.	.	.	0.91	-0.00	.	*	.	0.30	0.29
Val 219	.	A	B	B	.	.	.	0.80	-0.00	*	*	.	0.30	0.25
Phe 220	.	.	B	B	.	.	.	-0.06	-0.00	*	.	.	0.30	0.57
Gly 221	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp 222	A	-0.36	-0.07	*	.	.	0.50	0.63
Glu 223	A	-1.18	-0.03	*	.	.	0.50	0.60
Leu 224	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser 225	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu 226	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val 227	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr 228	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu 229	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe 230	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg 231	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys 232	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile 233	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln 234	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn 235	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met 236	.	.	.	B	.	.	C	0.01	-0.01	*	.	F	0.20	2.44
Pro 237	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu 238	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr 239	C	1.36	0.04	*	.	F	1.12	1.82
Leu 240	C	1.06	-0.17	*	.	F	1.96	1.89
Pro 241	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn 242	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn 243	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser 244	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys 245	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr 246	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser 247	A	-0.42	0.71	.	.	.	-0.40	0.18
Ala 248	A	A	-0.38	0.83	.	.	.	-0.60	0.34
Gly 249	A	A	-0.89	0.26	.	.	.	-0.30	0.43
Ile 250	A	A	-0.22	0.19	*	.	.	-0.30	0.27

Table 9 (continued)

Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala 251	A	A	0.02	-0.20	*	.	.	0.30	0.46
Lys 252	A	A	-0.02	-0.70	.	.	.	0.60	0.80
Leu 253	A	A	0.57	-0.70	.	.	F	0.90	1.13
Glu 254	A	A	0.91	-1.39	.	.	F	0.90	1.87
Glu 255	A	A	0.99	-1.89	.	.	F	0.90	1.62
Gly 256	A	A	1.58	-1.20	.	*	F	0.90	1.62
Asp 257	A	A	0.72	-1.49	.	*	F	0.90	1.62
Glu 258	A	A	0.94	-0.80	*	*	F	0.75	0.77
Leu 259	A	A	0.06	-0.30	*	*	.	0.30	0.79
Gln 260	A	A	-0.16	-0.04	*	.	.	0.30	0.33
Leu 261	A	A	0.30	0.39	*	.	.	-0.30	0.30
Ala 262	A	A	0.30	0.39	*	.	.	-0.30	0.70
Ile 263	A	A	0.30	-0.30	.	*	.	0.30	0.70
Pro 264	A	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg 265	A	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu 266	A	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn 267	A	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala 268	A	0.81	-0.63	*	*	.	0.95	1.05
Gln 269	A	1.02	0.06	*	*	.	-0.10	0.50
Ile 270	A	0.57	0.06	.	*	.	0.15	0.52
Ser 271	C	0.57	0.09	.	*	.	0.60	0.51
Leu 272	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp 273	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly 274	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp 275	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val 276	A	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr 277	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe 278	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe 279	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly 280	A	A	-1.58	0.67	.	*	.	-0.60	0.28
Ala 281	A	A	-1.53	0.87	.	*	.	-0.60	0.27
Leu 282	A	A	-1.61	0.77	*	.	.	-0.60	0.26
Lys 283	A	A	-1.30	0.41	*	.	.	-0.60	0.33
Leu 284	A	A	-0.99	0.41	.	.	.	-0.60	0.42
Leu 285	A	A	-1.03	0.34	*	.	.	-0.30	0.65

Table 10

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	T	T	.	1.09	-1.80	*	*	F	3.06	2.72
Asp	44	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	-2.00	1.23	.	.	.	-0.60	0.19

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	T	.	-0.50	0.16	.	.	.	0.10	0.55
Gln	73	A	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	0.66	-0.46	.	.	F	0.60	1.01

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	-0.80	0.49	*	*	.	-0.60	0.38
Thr	109	A	A	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	C	0.34	0.00	*	.	F	2.20	1.47
Ala	119	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	C	1.66	-0.60	*	.	F	1.15	0.89
Gln	136	C	1.66	-0.60	*	.	F	1.49	0.79
Gly	137	T	C	1.30	-0.60	*	.	F	2.18	1.35
Pro	138	T	C	0.84	-0.61	*	.	F	2.52	2.63
Glu	139	T	C	1.13	-0.83	*	.	F	2.86	1.50
Glu	140	T	T	.	1.74	-0.84	.	.	F	3.40	2.03
Thr	141	T	T	.	1.43	-0.51	.	.	F	2.86	2.06
Gly	142	T	T	.	1.08	-0.46	.	.	F	2.42	1.72
Ser	143	T	T	.	0.43	0.33	.	.	F	1.33	0.86
Tyr	144	T	T	.	0.22	0.97	.	.	.	0.54	0.44
Thr	145	T	T	.	-0.07	0.91	.	.	.	0.20	0.69
Phe	146	.	.	B	B	.	.	.	-0.57	1.40	.	.	.	-0.60	0.54
Val	147	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	148	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	149	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	150	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Leu	151	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ser	152	A	0.19	0.46	*	.	.	0.20	0.71
Phe	153	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	154	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	155	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	156	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	157	A	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	158	A	A	1.66	-1.00	*	.	F	1.35	0.76
Leu	159	A	A	1.61	-1.00	.	.	F	1.20	1.54
Glu	160	A	A	1.50	-1.43	.	.	F	0.90	1.98
Glu	161	A	A	1.89	-1.41	*	.	F	0.90	3.16
Lys	162	A	A	1.30	-1.91	*	.	F	0.90	7.66
Glu	163	A	A	1.08	-1.91	.	.	F	0.90	3.10
Asn	164	A	A	1.03	-1.23	*	*	F	0.90	1.48
Lys	165	A	A	1.08	-0.59	*	.	F	0.75	0.55
Ile	166	A	A	1.08	-0.59	*	*	.	0.60	0.63
Leu	167	A	A	0.72	-0.59	*	*	.	0.76	0.68
Val	168	A	A	0.38	-0.50	.	*	.	0.92	0.49
Lys	169	A	A	0.13	-0.07	*	*	F	0.93	0.69
Glu	170	A	T	.	-0.61	0.00	*	*	F	1.64	1.32
Thr	171	T	T	.	-0.42	0.10	.	*	F	1.60	1.54
Gly	172	T	T	.	-0.50	0.24	*	.	F	1.29	0.67
Tyr	173	T	T	.	0.11	0.93	*	*	.	0.68	0.27
Phe	174	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.28	0.29
Phe	175	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.44	0.29
Ile	176	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	177	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	178	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	179	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	180	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	181	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92
Tyr	182	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	183	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	184	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	185	A	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	186	A	A	0.90	-0.16	.	.	F	0.60	1.73
Tyr	187	A	A	1.11	-0.21	.	.	.	0.45	1.03
Ala	188	A	A	0.61	0.29	.	.	.	-0.30	0.70
Met	189	A	A	-0.28	0.97	.	.	.	-0.60	0.40
Gly	190	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	191	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu	192	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	193	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	194	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	195	A	A	.	B	.	.	.	1.08	-0.59	*	*	F	0.90	1.62
Lys	196	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	197	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	198	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	199	.	A	B	B	.	.	.	0.91	0.00	*	*	.	0.30	0.29
Val	200	.	A	B	B	.	.	.	0.80	0.00	*	*	.	0.30	0.25

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Phe	201	.	.	B	B	.	.	.	-0.06	0.00	*	.	.	0.30	0.57
Gly	202	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	203	A	-0.36	-0.07	*	.	.	0.50	0.63
Glu	204	A	-1.18	-0.03	*	.	.	0.50	0.60
Leu	205	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	206	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	207	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	208	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	209	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	210	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	211	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	212	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	213	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	214	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	215	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	216	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	217	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	218	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	219	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	220	C	1.36	0.04	*	.	F	1.12	1.82
Leu	221	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	222	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	223	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	224	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	225	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	226	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	227	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	228	A	-0.42	0.71	.	.	.	-0.40	0.18
Ala	229	A	A	-0.38	0.83	.	.	.	-0.60	0.34
Gly	230	A	A	-0.89	0.26	.	.	.	-0.30	0.43
Ile	231	A	A	-0.22	0.19	*	.	.	-0.30	0.27
Ala	232	A	A	0.02	-0.20	*	.	.	0.30	0.46
Lys	233	A	A	-0.02	-0.70	.	.	.	0.60	0.80
Leu	234	A	A	0.57	-0.70	.	.	F	0.90	1.13
Glu	235	A	A	0.91	-1.39	.	.	F	0.90	1.87
Glu	236	A	A	0.99	-1.89	.	.	F	0.90	1.62
Gly	237	A	A	1.58	-1.20	.	*	F	0.90	1.62
Asp	238	A	A	0.72	-1.49	.	*	F	0.90	1.62
Glu	239	A	A	0.94	-0.80	*	*	F	0.75	0.77
Leu	240	A	A	0.06	-0.30	*	*	.	0.30	0.79
Gln	241	A	A	-0.16	-0.04	*	.	.	0.30	0.33
Leu	242	A	A	0.30	0.39	*	.	.	-0.30	0.30
Ala	243	A	A	0.30	0.39	*	.	.	-0.30	0.70
Ile	244	A	A	0.30	-0.30	.	*	.	0.30	0.70
Pro	245	A	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	246	A	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	247	A	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	248	A	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	249	A	0.81	-0.63	*	*	.	0.95	1.05
Gln	250	A	1.02	0.06	*	*	.	-0.10	0.50

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ile	251	A	0.57	0.06	*	*	.	0.15	0.52
Ser	252	C	0.57	0.09	.	*	.	0.60	0.51
Leu	253	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	254	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	255	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	256	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	257	A	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	258	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	259	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	260	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	261	A	A	-1.58	0.67	.	*	.	-0.60	0.28
Ala	262	A	A	-1.53	0.87	.	*	.	-0.60	0.27
Leu	263	A	A	-1.61	0.77	*	.	.	-0.60	0.26
Lys	264	A	A	-1.30	0.41	*	.	.	-0.60	0.33
Leu	265	A	A	-0.99	0.41	.	.	.	-0.60	0.42
Leu	266	A	A	-1.03	0.34	*	.	.	-0.30	0.65

[0093] In another embodiment, the invention provides antibodies that bind a polypeptide comprising, or alternatively consisting of, an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion may be an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1983).

[0094] As to the selection of polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) "Antibodies that react with predetermined sites on proteins", *Science*, 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson *et al.*, *Cell* 37:767-778 (1984) at 777.

[0095] In specific embodiments, antibodies of the present invention bind antigenic epitope-bearing peptides and polypeptides of BLYS and preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids contained within the amino acid sequence of a BLYS polypeptide. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.

[0096] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLYS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-115 to about Leu-147 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-150 to about Tyr-163 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-171 to about Phe-194 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-223 to about Tyr-246 in SEQ ID NO:3228; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-271 to about Phe-278 in Figures 1A and 1B (SEQ ID NO:3228). In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLYS polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed Table 9, above.

[0097] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLYS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-32 to about Leu-47 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-116 to about Ser-143 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-153 to about Tyr-173 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-218 to about Tyr-227 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ala-232 to about Gln-241 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-244 to about Ala-249 in SEQ ID NO:3229; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-252 to about Val-257 in SEQ ID NO:3229. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLYS polypeptide by the analysis of the Jameson-Wolf

antigenic index, as disclosed in Table 10 generated by the Protean component of the DNA*STAR computer program (as set forth above).

[0098] BLYS epitope-bearing peptides and polypeptides may be produced by any conventional means. *See, e.g.*, Houghten, R. A. (1985) General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc. Natl. Acad. Sci. USA* 82:5131-5135; this "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U. S. Patent No. 4,631,211 to Houghten et al. (1986).

[0099] The present invention encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3228, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 97768, or encoded by a polynucleotide that hybridizes to cDNA sequence contained in ATCC deposit No. 97768 (e.g., under hybridization conditions described herein).

[0100] The present invention also encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3229, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 203518, or encoded by a polynucleotide that hybridizes to the cDNA sequence contained in ATCC deposit No. 203518 (e.g., under hybridization conditions described herein).

[0101] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses antibodies that bind a polypeptide comprising an epitope. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not

necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0102] BLYS polypeptide fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

[0103] In the present invention, antibodies of the present invention bind antigenic epitopes preferably containing a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes that may be bound by antibodies of the present invention are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0104] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985)). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes of BLYS may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise

antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0105] Epitope-bearing BLYS polypeptides may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 micrograms of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0106] As one of skill in the art will appreciate, and as discussed above, the antibodies of the present invention may bind polypeptides comprising an immunogenic or antigenic epitope fused to other polypeptide sequences. For example, the BLYS polypeptides may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins

consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix-binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni^{2+} nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

[0107] In another embodiment, the antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with a heterologous antigen (e.g., polypeptide, carbohydrate, phospholipid, or nucleic acid). In specific embodiments, the heterologous antigen is an immunogen.

[0108] In a more specific embodiment, the heterologous antigen is the gp120 protein of HIV, or a fragment thereof.

[0109] In another embodiment, antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with polypeptide sequences of another TNF ligand family member (or biologically active fragments or variants thereof). In a specific embodiment, the antibodies of the present invention bind BLyS polypeptides of the present invention are fused with a CD40L polypeptide sequence. In a preferred embodiment, the CD40L polypeptide sequence is soluble.

[0110] In another embodiment, antibodies of the present invention bind mutant BLyS polypeptides that have been generated by random mutagenesis of a polynucleotide encoding the BLyS polypeptide, by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, antibodies of the present invention bind one or more components, motifs, sections, parts, domains, fragments, etc., of BLyS recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are, for example, TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190), endokine-alpha (International Publication No. WO 98/07880), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), TR12, CAD, and v-FLIP. In further embodiments, the heterologous molecules are any member of the TNF family.

[0111] In another preferred embodiment, antibodies of the present invention bind BLyS polypeptides of the invention (including biologically active fragments or variants thereof), that are fused with soluble APRIL polypeptides (e.g., amino acid residues 105 through 250 of SEQ ID NO:3239), or biologically active fragments or variants thereof.

[0112] To improve or alter the characteristics of BLyS polypeptides, protein engineering may be employed. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. For instance, for

many proteins, including the extracellular domain or the mature form(s) of a secreted protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al., J. Biol. Chem., 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing. Accordingly, antibodies of the present invention may bind BLyS polypeptide mutants or variants generated by protein engineering.

[0113] In the present case, since the protein of the invention is a member of the TNF polypeptide family, deletions of N-terminal amino acids up to the Gly (G) residue at position 191 in SEQ ID NO:3228 may retain some biological activity such as, for example, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and cytotoxicity to appropriate target cells. Polypeptides having further N-terminal deletions including the Gly (G) residue would not be expected to retain biological activities because it is known that this residue in TNF-related polypeptides is in the beginning of the conserved domain required for biological activities. However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or extracellular domain of the protein generally will be retained when less than the majority of the residues of the complete or extracellular domain of the protein are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0114] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the BLyS of SEQ ID NO:3228, up to the glycine residue at position 191 (Gly-191 residue from the amino terminus). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1 -285 of SEQ ID NO:3228, where n^1 is an integer in the range of the amino acid position of amino acid residues 2-190 of the amino acid sequence in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind polypeptides

comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 2-285, 3-285, 4-285, 5-285, 6-285, 7-285, 8-285, 9-285, 10-285, 11-285, 12-285, 13-285, 14-285, 15-285, 16-285, 17-285, 18-285, 19-285, 20-285, 21-285, 22-285, 23-285, 24-285, 25-285, 26-285, 27-285, 28-285, 29-285, 30-285, 31-285, 32-285, 33-285, 34-285, 35-285, 36-285, 37-285, 38-285, 39-285, 40-285, 41-285, 42-285, 43-285, 44-285, 45-285, 46-285, 47-285, 48-285, 49-285, 50-285, 51-285, 52-285, 53-285, 54-285, 55-285, 56-285, 57-285, 58-285, 59-285, 60-285, 61-285, 62-285, 63-285, 64-285, 65-285, 66-285, 67-285, 68-285, 69-285, 70-285, 71-285, 72-285, 73-285, 74-285, 75-285, 76-285, 77-285, 78-285, 79-285, 80-285, 81-285, 82-285, 83-285, 84-285, 85-285, 86-285, 87-285, 88-285, 89-285, 90-285, 91-285, 92-285, 93-285, 94-285, 95-285, 96-285, 97-285, 98-285, 99-285, 100-285, 101-285, 102-285, 103-285, 104-285, 105-285, 106-285, 107-285, 108-285, 109-285, 110-285, 111-285, 112-285, 113-285, 114-285, 115-285, 116-285, 117-285, 118-285, 119-285, 120-285, 121-285, 122-285, 123-285, 124-285, 125-285, 126-285, 127-285, 128-285, 129-285, 130-285, 131-285, 132-285, 133-285, 134-285, 135-285, 136-285, 137-285, 138-285, 139-285, 140-285, 141-285, 142-285, 143-285, 144-285, 145-285, 146-285, 147-285, 148-285, 149-285, 150-285, 151-285, 152-285, 153-285, 154-285, 155-285, 156-285, 157-285, 158-285, 159-285, 160-285, 161-285, 162-285, 163-285, 164-285, 165-285, 166-285, 167-285, 168-285, 169-285, 170-285, 171-285, 172-285, 173-285, 174-285, 175-285, 176-285, 177-285, 178-285, 179-285, 180-285, 181-285, 182-285, 183-285, 184-285, 185-285, 186-285, 187-285, 188-285, 189-285, and 190-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0115] Furthermore, since the predicted extracellular domain of the BLyS polypeptides of the invention may itself elicit biological activity, deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide (spanning positions Gln-73 to Leu-285 of SEQ ID NO:3228) may retain some biological activity such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. However, even if deletion of one or more amino acids

from the N-terminus of the predicted extracellular domain of a BLyS polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0116] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3228, up to the glycine residue at position number 280. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^2 -285 of SEQ ID NO:3228, where n^2 is an integer in the range of the amino acid position of amino acid residues 73-280 in SEQ ID NO:3228, and 73 is the position of the first residue from the N-terminus of the predicted extracellular domain of the BLyS polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to

L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

[0117] Highly preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence least 80%, 85%, 90% identical and more preferably at least 95%, 96%, 97%, 98%, 99% or 100% identical to BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0118] Preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 90% identical to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 95% identical to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 96% identical to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0119] Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 97% to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 98% to a BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 99% identical to BLYS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0120] In specific embodiments, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, one of the following N-terminally deleted polypeptide fragments of BLYS: amino acid residues Ala-71 through Leu-285, amino acid residues Ala-81 through Leu-285, amino acid residues Leu-112 through Leu-285, amino

acid residues Ala-134 through Leu-285, amino acid residues Leu-147 through Leu-285, and amino acid residues Gly-161 through Leu-285 of SEQ ID NO:3228.

[0121] Similarly, many examples of biologically functional C-terminal deletion polypeptides are known. For instance, Interferon gamma shows up to ten times higher activities by deleting 8-10 amino acid residues from the carboxy terminus of the protein (Döbeli et al., *J. Biotechnology* 7:199-216 (1988)). Since the present protein is a member of the TNF polypeptide family, deletions of C-terminal amino acids up to the leucine residue at position 284 are expected to retain most if not all biological activity such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication. Polypeptides having deletions of up to about 10 additional C-terminal residues (i.e., up to the glycine residue at position 274) also may retain some activity such as receptor binding, although such polypeptides would lack a portion of the conserved TNF domain which extends to about Leu-284 of SEQ ID NO:3228. However, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or mature protein generally will be retained when less than the majority of the residues of the complete or mature protein are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0122] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS polypeptide of SEQ ID NO:3228, up to the glycine residue at position 274 (Gly-274). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m¹ of the amino acid sequence in SEQ ID NO:3228, where m¹ is any integer in the range of the amino acid position of amino acid residues 274-284 in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind BLyS polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 1-274, 1-275, 1-276, 1-277, 1-278, 1-279, 1-280, 1-281, 1-282,

1-283 and 1-284 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0123] Also provided are antibodies that bind BLyS polypeptides comprising, or alternatively consisting of, BLyS polypeptides with one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n^1 - m^1 of SEQ ID NO:3228, where n^1 and m^1 are integers as defined above. Also included are antibodies that bind a polypeptide comprising, or alternatively consisting of, a portion of the complete BLyS amino acid sequence encoded by the deposited cDNA clone contained in ATCC Accession No. 97768 where this portion excludes from 1 to 190 amino acids from the amino terminus or from 1 to 11 amino acids from the C-terminus of the complete amino acid sequence (or any combination of these N-terminal and C-terminal deletions) encoded by the cDNA clone in the deposited plasmid.

[0124] Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLyS up to the leucine residue at position 79 of SEQ ID NO:3228 may retain some biological activity, such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3228 would not be expected to retain biological activities.

[0125] However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0126] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLyS polypeptide shown in SEQ ID NO:3228, up to the leucine residue at position 79 of SEQ ID NO:3228. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 73- m^2 of the amino acid sequence in SEQ ID NO:3228, where m^2 is any integer in the range of the amino acid position of amino acid residues 79 to 285 in the amino acid sequence in SEQ ID NO:3228, and residue 78 is the position of the first residue at the C- terminus of the predicted extracellular domain of the BLyS polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to Leu-285; Q-73 to L-284; Q-73 to K-283; Q-73 to L-282; Q-73 to A-281; Q-73 to G-280; Q-73 to F-279; Q-73 to F-278; Q-73 to T-277; Q-73 to V-276; Q-73 to D-275; Q-73 to G-274; Q-73 to D-273; Q-73 to L-272; Q-73 to S-271; Q-73 to I-270; Q-73 to Q-269; Q-73 to A-268; Q-73 to N-267; Q-73 to E-266; Q-73 to R-265; Q-73 to P-264; Q-73 to I-263; Q-73 to A-262; Q-73 to L-261; Q-73 to Q-260; Q-73 to L-259; Q-73 to E-258; Q-73 to D-257; Q-73 to G-256; Q-73 to E-255; Q-73 to E-254; Q-73 to L-253; Q-73 to K-252; Q-73 to A-251; Q-73 to I-250; Q-73 to G-249; Q-73 to A-248; Q-73 to S-247; Q-73 to Y-246; Q-73 to C-245; Q-73 to S-244; Q-73 to N-243; Q-73 to N-242; Q-73 to P-241; Q-73 to L-240; Q-73 to T-239; Q-73 to E-238; Q-73 to P-237; Q-73 to M-236; Q-73 to N-235; Q-73 to Q-234; Q-73 to I-233; Q-73 to C-232; Q-73 to R-231; Q-73 to F-230; Q-73 to L-229; Q-73 to T-228; Q-73 to V-227; Q-73 to L-226; Q-73 to S-225; Q-73 to L-224; Q-73 to E-223; Q-73 to D-222; Q-73 to G-221; Q-73 to F-220; Q-73 to V-219; Q-73 to H-218; Q-73 to V-217; Q-73 to K-216; Q-73 to K-215; Q-73 to R-214; Q-73 to Q-213; Q-73 to I-212; Q-73 to L-211; Q-73 to H-210; Q-73 to G-209; Q-73 to M-208; Q-73 to A-207; Q-73 to Y-206; Q-73 to T-205; Q-73 to K-204; Q-73 to D-203; Q-73 to T-202; Q-73 to Y-201; Q-73 to L-200; Q-73 to V-199; Q-73 to Q-198; Q-73 to G-197; Q-73 to Y-196; Q-73 to I-195; Q-73 to F-194; Q-73 to F-193; Q-73 to Y-192; Q-73 to G-191; Q-73 to T-190; Q-73 to E-189; Q-73 to K-188; Q-73 to V-187; Q-73 to L-186; Q-73 to I-185; Q-73 to K-184; Q-73 to N-183; Q-73 to E-182; Q-73 to K-181; Q-73 to E-180; Q-73 to E-179; Q-73 to L-178;

Q-73 to A-177; Q-73 to S-176; Q-73 to G-175; Q-73 to R-174; Q-73 to K-173; Q-73 to F-172; Q-73 to S-171; Q-73 to L-170; Q-73 to L-169; Q-73 to W-168; Q-73 to P-167; Q-73 to V-166; Q-73 to F-165; Q-73 to T-164; Q-73 to Y-163; Q-73 to S-162; Q-73 to G-161; Q-73 to K-160; Q-73 to Q-159; Q-73 to I-158; Q-73 to T-157; Q-73 to P-156; Q-73 to T-155; Q-73 to E-154; Q-73 to S-153; Q-73 to D-152; Q-73 to A-151; Q-73 to I-150; Q-73 to L-149; Q-73 to Q-148; Q-73 to L-147; Q-73 to C-146; Q-73 to D-145; Q-73 to Q-144; Q-73 to T-143; Q-73 to V-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; and Q-73 to L-79 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0127] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLyS, which may be described generally as having residues n^2 - m^2 of SEQ ID NO:3228 where n^2 and m^2 are integers as defined above.

[0128] In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLyS amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, where this portion excludes from 1 to about 206 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, or from 1 to about

206 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC accession no. 97768.

[0129] As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functions or biological activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted N-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0130] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLyS shown in SEQ ID NO:3228, up to the glycine residue at position number 280 of the sequence shown SEQ ID NO:3228 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^3 -285 of the sequence shown in SEQ ID NO:3228, where n^3 is an integer in the range of the amino acid position of amino acid residues 1 to 280 of the amino acid sequence in SEQ ID NO:3228.

[0131] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-285; D-3 to L-285; S-4 to L-285; T-5 to L-285; E-6 to L-285; R-7 to L-285; E-8 to L-285; Q-9 to L-285; S-10 to L-285; R-11 to L-285; L-12 to

L-285; T-13 to L-285; S-14 to L-285; C-15 to L-285; L-16 to L-285; K-17 to L-285; K-18 to L-285; R-19 to L-285; E-20 to L-285; E-21 to L-285; M-22 to L-285; K-23 to L-285; L-24 to L-285; K-25 to L-285; E-26 to L-285; C-27 to L-285; V-28 to L-285; S-29 to L-285; I-30 to L-285; L-31 to L-285; P-32 to L-285; R-33 to L-285; K-34 to L-285; E-35 to L-285; S-36 to L-285; P-37 to L-285; S-38 to L-285; V-39 to L-285; R-40 to L-285; S-41 to L-285; S-42 to L-285; K-43 to L-285; D-44 to L-285; G-45 to L-285; K-46 to L-285; L-47 to L-285; L-48 to L-285; A-49 to L-285; A-50 to L-285; T-51 to L-285; L-52 to L-285; L-53 to L-285; L-54 to L-285; A-55 to L-285; L-56 to L-285; L-57 to L-285; S-58 to L-285; C-59 to L-285; C-60 to L-285; L-61 to L-285; T-62 to L-285; V-63 to L-285; V-64 to L-285; S-65 to L-285; F-66 to L-285; Y-67 to L-285; Q-68 to L-285; V-69 to L-285; A-70 to L-285; A-71 to L-285; L-72 to L-285; Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to

L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

[0132] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activity) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLYS mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLYS

mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0133] Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3228, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m³ of SEQ ID NO:3228, where m³ is an integer in the range of the amino acid position of amino acid residues 6-284 of the amino acid sequence in SEQ ID NO:3228.

[0134] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-284; M-1 to K-283; M-1 to L-282; M-1 to A-281; M-1 to G-280; M-1 to F-279; M-1 to F-278; M-1 to T-277; M-1 to V-276; M-1 to D-275; M-1 to G-274; M-1 to D-273; M-1 to L-272; M-1 to S-271; M-1 to I-270; M-1 to Q-269; M-1 to A-268; M-1 to N-267; M-1 to E-266; M-1 to R-265; M-1 to P-264; M-1 to I-263; M-1 to A-262; M-1 to L-261; M-1 to Q-260; M-1 to L-259; M-1 to E-258; M-1 to D-257; M-1 to G-256; M-1 to E-255; M-1 to E-254; M-1 to L-253; M-1 to K-252; M-1 to A-251; M-1 to I-250; M-1 to G-249; M-1 to A-248; M-1 to S-247; M-1 to Y-246; M-1 to C-245; M-1 to S-244; M-1 to N-243; M-1 to N-242; M-1 to P-241; M-1 to L-240; M-1 to T-239; M-1 to E-238; M-1 to P-237; M-1 to M-236; M-1 to N-235; M-1 to Q-234; M-1 to I-233; M-1 to C-232; M-1 to R-231; M-1 to F-230; M-1 to L-229; M-1 to T-228; M-1 to V-227; M-1 to L-226; M-1 to S-225; M-1 to L-224; M-1 to E-223; M-1 to D-222; M-1 to G-221; M-1 to F-220; M-1 to V-219; M-1 to H-218; M-1 to V-217; M-1 to K-216; M-1 to K-215; M-1 to R-214; M-1 to Q-213; M-1 to I-212; M-1 to L-211; M-1 to H-210; M-1 to G-209; M-1 to M-208; M-1 to A-207; M-1 to Y-206; M-1 to T-205; M-1 to K-204; M-1 to D-203; M-1 to T-202; M-1 to Y-201; M-1 to L-200; M-1 to V-199; M-1 to Q-198; M-1 to G-197; M-1 to Y-196; M-1 to I-195; M-1 to F-194; M-1 to F-193; M-1 to Y-192; M-1 to G-191; M-1 to T-190; M-1 to E-189; M-1 to K-188; M-1 to V-187; M-1 to L-186; M-1 to I-185; M-1 to K-184; M-1 to N-183; M-1 to E-182; M-1 to K-181; M-1 to E-180; M-1 to E-179; M-1 to L-178; M-1 to A-177; M-1 to S-176; M-1 to G-175; M-1 to R-174; M-1 to K-173; M-1 to

F-172; M-1 to S-171; M-1 to L-170; M-1 to L-169; M-1 to W-168; M-1 to P-167; M-1 to V-166; M-1 to F-165; M-1 to T-164; M-1 to Y-163; M-1 to S-162; M-1 to G-161; M-1 to K-160; M-1 to Q-159; M-1 to I-158; M-1 to T-157; M-1 to P-156; M-1 to T-155; M-1 to E-154; M-1 to S-153; M-1 to D-152; M-1 to A-151; M-1 to I-150; M-1 to L-149; M-1 to Q-148; M-1 to L-147; M-1 to C-146; M-1 to D-145; M-1 to Q-144; M-1 to T-143; M-1 to V-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0135] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues n^3 - m^3 of SEQ ID NO:3228, where n^3 and m^3 are integers as defined above.

[0136] Furthermore, since the predicted extracellular domain of the BLyS polypeptide of SEQ ID NO:3229 may itself elicit functional activity (e.g., biological activity), deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide at positions Gln-73 to Leu-266 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, to stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLyS polypeptide results in modification or loss of one or more functional activities of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0137] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3229, up to the glycine residue at position number 261. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^4 -266 of SEQ ID NO:3229, where n^4 is an integer in the range of the amino acid position of amino acid residues 73-261 of the amino acid sequence in SEQ ID NO:3229, and 261 is the position of the first residue from the N-terminus of the predicted extracellular domain BLyS polypeptide (shown in SEQ ID NO:3229).

[0138] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence

selected from the group consisting of residues of Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240

to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

[0139] Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLYS up to the leucine residue at position 79 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3229 would not be expected to retain biological activities.

[0140] However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0141] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLYS shown in SEQ ID NO:3229, up to the leucine residue at position 79 of SEQ ID NO:3229. In particular, the present invention provides antibodies that bind polypeptides having the amino acid sequence of residues 73-m⁴ of the amino acid sequence in SEQ ID NO:3229, where m⁴ is any integer in the

range of the amino acid position of amino acid residues 79-265 of the amino acid sequence in SEQ ID NO:3229.

[0142] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to L-265; Q-73 to K-264; Q-73 to L-263; Q-73 to A-262; Q-73 to G-261; Q-73 to F-260; Q-73 to F-259; Q-73 to T-258; Q-73 to V-257; Q-73 to D-256; Q-73 to G-255; Q-73 to D-254; Q-73 to L-253; Q-73 to S-252; Q-73 to I-251; Q-73 to Q-250; Q-73 to A-249; Q-73 to N-248; Q-73 to E-247; Q-73 to R-246; Q-73 to P-245; Q-73 to I-244; Q-73 to A-243; Q-73 to L-242; Q-73 to Q-241; Q-73 to L-240; Q-73 to E-239; Q-73 to D-238; Q-73 to G-237; Q-73 to E-236; Q-73 to E-235; Q-73 to L-234; Q-73 to K-233; Q-73 to A-232; Q-73 to I-231; Q-73 to G-230; Q-73 to A-229; Q-73 to S-228; Q-73 to Y-227; Q-73 to C-226; Q-73 to S-225; Q-73 to N-224; Q-73 to N-223; Q-73 to P-222; Q-73 to L-221; Q-73 to T-220; Q-73 to E-219; Q-73 to P-218; Q-73 to M-217; Q-73 to N-216; Q-73 to Q-215; Q-73 to I-214; Q-73 to C-213; Q-73 to R-212; Q-73 to F-211; Q-73 to L-210; Q-73 to T-209; Q-73 to V-208; Q-73 to L-207; Q-73 to S-206; Q-73 to L-205; Q-73 to E-204; Q-73 to D-203; Q-73 to G-202; Q-73 to F-201; Q-73 to V-200; Q-73 to H-199; Q-73 to V-198; Q-73 to K-197; Q-73 to K-196; Q-73 to R-195; Q-73 to Q-194; Q-73 to I-193; Q-73 to L-192; Q-73 to H-191; Q-73 to G-190; Q-73 to Q-7389; Q-73 to A-188; Q-73 to Y-187; Q-73 to T-186; Q-73 to K-185; Q-73 to D-184; Q-73 to T-183; Q-73 to Y-182; Q-73 to L-181; Q-73 to V-180; Q-73 to Q-179; Q-73 to G-178; Q-73 to Y-177; Q-73 to I-176; Q-73 to F-175; Q-73 to F-174; Q-73 to Y-173; Q-73 to G-172; Q-73 to T-171; Q-73 to E-170; Q-73 to K-169; Q-73 to V-168; Q-73 to L-167; Q-73 to I-166; Q-73 to K-165; Q-73 to N-164; Q-73 to E-163; Q-73 to K-162; Q-73 to E-161; Q-73 to E-160; Q-73 to L-159; Q-73 to A-158; Q-73 to S-157; Q-73 to G-156; Q-73 to R-155; Q-73 to K-154; Q-73 to F-153; Q-73 to S-152; Q-73 to L-151; Q-73 to L-150; Q-73 to W-149; Q-73 to P-148; Q-73 to V-147; Q-73 to F-146; Q-73 to T-145; Q-73 to Y-144; Q-73 to S-143; Q-73 to G-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115;

Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; Q-73 to L-79; and Q-73 to S-78 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

[0143] The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLYS, which may be described generally as having residues n^4 - m^4 of SEQ ID NO:3229 where n^4 and m^4 are integers as defined above.

[0144] In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLYS amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Accession No. 203518, where this portion excludes from 1 to about 260 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or from 1 to about 187 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Accession No. 203518.

[0145] As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of a shortened BLYS polypeptide to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of

the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted N-terminal amino acid residues may retain functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0146] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLyS polypeptide shown in SEQ ID NO:3229, up to the glycine residue at position number 261 of the sequence shown SEQ ID NO:3229 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^5 -266 of the sequence shown in SEQ ID NO:3229, where n^5 is an integer in the range of the amino acid position of amino acid residues 1 to 261 of the amino acid sequence in SEQ ID NO:3229.

[0147] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-266; D-3 to L-266; S-4 to L-266; T-5 to L-266; E-6 to L-266; R-7 to L-266; E-8 to L-266; Q-9 to L-266; S-10 to L-266; R-11 to L-266; L-12 to L-266; T-13 to L-266; S-14 to L-266; C-15 to L-266; L-16 to L-266; K-17 to L-266; K-18 to L-266; R-19 to L-266; E-20 to L-266; E-21 to L-266; M-22 to L-266; K-23 to L-266; L-24 to L-266; K-25 to L-266; E-26 to L-266; C-27 to L-266; V-28 to L-266; S-29 to L-266; I-30 to L-266; L-31 to L-266; P-32 to L-266; R-33 to L-266; K-34 to L-266; E-35 to L-266; S-36 to L-266; P-37 to L-266; S-38 to L-266; V-39 to L-266; R-40 to L-266; S-41 to L-266; S-42 to L-266; K-43 to L-266; D-44 to L-266; G-45 to L-266; K-46 to L-266; L-47 to L-266; L-48 to L-266; A-49 to L-266; A-50 to L-266; T-51 to L-266; L-52 to L-266; L-53 to L-266; L-54 to L-266; A-55 to L-266; L-56 to L-266; L-57 to L-266; S-58 to L-266; C-59 to L-266; C-60 to L-266; L-61 to L-266; T-62 to L-266; V-63 to L-266; V-64 to L-266; S-65 to L-266; F-66 to L-266; Y-67 to L-266; Q-68 to L-266; V-69 to L-266; A-70 to L-266; A-71 to L-266; L-72 to L-266; Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to

L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to

L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0148] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activities) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0149] Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3229, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m⁵ of SEQ ID NO:3229, where m⁵ is an integer in the range of the amino acid position of amino acid residues 6 to 265 in the amino acid sequence of SEQ ID NO:3229.

[0150] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-265; M-1 to K-264; M-1 to L-263; M-1 to A-262; M-1 to G-261; M-1 to F-260; M-1 to F-259; M-1 to T-258; M-1 to V-257; M-1 to D-256; M-1 to G-255; M-1 to D-254; M-1 to L-253; M-1 to S-252; M-1 to I-251; M-1 to Q-250; M-1 to

A-249; M-1 to N-248; M-1 to E-247; M-1 to R-246; M-1 to P-245; M-1 to I-244; M-1 to A-243; M-1 to L-242; M-1 to Q-241; M-1 to L-240; M-1 to E-239; M-1 to D-238; M-1 to G-237; M-1 to E-236; M-1 to E-235; M-1 to L-234; M-1 to K-233; M-1 to A-232; M-1 to I-231; M-1 to G-230; M-1 to A-229; M-1 to S-228; M-1 to Y-227; M-1 to C-226; M-1 to S-225; M-1 to N-224; M-1 to N-223; M-1 to P-222; M-1 to L-221; M-1 to T-220; M-1 to E-219; M-1 to P-218; M-1 to M-217; M-1 to N-216; M-1 to Q-215; M-1 to I-214; M-1 to C-213; M-1 to R-212; M-1 to F-211; M-1 to L-210; M-1 to T-209; M-1 to V-208; M-1 to L-207; M-1 to S-206; M-1 to L-205; M-1 to E-204; M-1 to D-203; M-1 to G-202; M-1 to F-201; M-1 to V-200; M-1 to H-199; M-1 to V-198; M-1 to K-197; M-1 to K-196; M-1 to R-195; M-1 to Q-194; M-1 to I-193; M-1 to L-192; M-1 to H-191; M-1 to G-190; M-1 to M-189; M-1 to A-188; M-1 to Y-187; M-1 to T-186; M-1 to K-185; M-1 to D-184; M-1 to T-183; M-1 to Y-182; M-1 to L-181; M-1 to V-180; M-1 to Q-179; M-1 to G-178; M-1 to Y-177; M-1 to I-176; M-1 to F-175; M-1 to F-174; M-1 to Y-173; M-1 to G-172; M-1 to T-171; M-1 to E-170; M-1 to K-169; M-1 to V-168; M-1 to L-167; M-1 to I-166; M-1 to K-165; M-1 to N-164; M-1 to E-163; M-1 to K-162; M-1 to E-161; M-1 to E-160; M-1 to L-159; M-1 to A-158; M-1 to S-157; M-1 to G-156; M-1 to R-155; M-1 to K-154; M-1 to F-153; M-1 to S-152; M-1 to L-151; M-1 to L-150; M-1 to W-149; M-1 to P-148; M-1 to V-147; M-1 to F-146; M-1 to T-145; M-1 to Y-144; M-1 to S-143; M-1 to G-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54;

M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0151] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues n^5 - m^5 of SEQ ID NO:3229, where n^5 and m^5 are integers as defined above.

[0152] In additional embodiments, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 134- m^6 of SEQ ID NO:3228, where m^6 is an integer from 140 to 285, corresponding to the position of the amino acid residue in SEQ ID NO:3228. For example, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues A-134 to Leu-285; A-134 to L-284; A-134 to K-283; A-134 to L-282; A-134 to A-281; A-134 to G-280; A-134 to F-279; A-134 to F-278; A-134 to T-277; A-134 to V-276; A-134 to D-275; A-134 to G-274; A-134 to D-273; A-134 to L-272; A-134 to S-271; A-134 to I-270; A-134 to Q-269; A-134 to A-268; A-134 to N-267; A-134 to E-266; A-134 to R-265; A-134 to P-264; A-134 to I-263; A-134 to A-262; A-134 to L-261; A-134 to Q-260; A-134 to L-259; A-134 to E-258; A-134 to D-257; A-134 to G-256; A-134 to E-255; A-134 to E-254; A-134 to L-253; A-134 to K-252; A-134 to A-251; A-134 to I-250; A-134 to G-249; A-134 to A-248; A-134 to S-247; A-134 to Y-246; A-134 to C-245; A-134 to S-244; A-134 to N-243; A-134 to N-242; A-134 to P-241; A-134 to L-240; A-134 to T-239; A-134 to E-238; A-134 to P-237; A-134 to M-236; A-134 to N-235; A-134 to Q-234; A-134 to

I-233; A-134 to C-232; A-134 to R-231; A-134 to F-230; A-134 to L-229; A-134 to T-228; A-134 to V-227; A-134 to L-226; A-134 to S-225; A-134 to L-224; A-134 to E-223; A-134 to D-222; A-134 to G-221; A-134 to F-220; A-134 to V-219; A-134 to H-218; A-134 to V-217; A-134 to K-216; A-134 to K-215; A-134 to R-214; A-134 to Q-213; A-134 to I-212; A-134 to L-211; A-134 to H-210; A-134 to G-209; A-134 to M-208; A-134 to A-207; A-134 to Y-206; A-134 to T-205; A-134 to K-204; A-134 to D-203; A-134 to T-202; A-134 to Y-201; A-134 to L-200; A-134 to V-199; A-134 to Q-198; A-134 to G-197; A-134 to Y-196; A-134 to I-195; A-134 to F-194; A-134 to F-193; A-134 to Y-192; A-134 to G-191; A-134 to T-190; A-134 to E-189; A-134 to K-188; A-134 to V-187; A-134 to L-186; A-134 to I-185; A-134 to K-184; A-134 to N-183; A-134 to E-182; A-134 to K-181; A-134 to E-180; A-134 to E-179; A-134 to L-178; A-134 to A-177; A-134 to S-176; A-134 to G-175; A-134 to R-174; A-134 to K-173; A-134 to F-172; A-134 to S-171; A-134 to L-170; A-134 to L-169; A-134 to W-168; A-134 to P-167; A-134 to V-166; A-134 to F-165; A-134 to T-164; A-134 to Y-163; A-134 to S-162; A-134 to G-161; A-134 to K-160; A-134 to Q-159; A-134 to I-158; A-134 to T-157; A-134 to P-156; A-134 to T-155; A-134 to E-154; A-134 to S-153; A-134 to D-152; A-134 to A-151; A-134 to I-150; A-134 to L-149; A-134 to Q-148; A-134 to L-147; A-134 to C-146; A-134 to D-145; A-134 to Q-144; A-134 to T-143; A-134 to V-142; A-134 to T-141; and A-134 to E-140 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0153] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42

to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to V-142; S-129 to T-143; R-130 to Q-144; N-131 to D-145; K-132 to C-146; R-133 to L-147; A-134 to Q-148; V-135 to L-149; Q-136 to I-150; G-137 to A-151; P-138 to D-152; E-139 to S-153; E-140 to E-154; T-141 to T-155; V-142 to P-156; T-143 to T-157; Q-144 to I-158; D-145 to Q-159; C-146 to K-160; L-147 to G-161; Q-148 to S-162; L-149 to Y-163; I-150 to T-164; A-151 to F-165; D-152 to V-166; S-153 to P-167; E-154 to W-168; T-155 to L-169; P-156 to L-170; T-157 to S-171; I-158 to F-172; Q-159 to K-173; K-160 to R-174; G-161 to G-175; S-162 to S-176; Y-163 to A-177; T-164 to L-178; F-165 to E-179; V-166 to E-180; P-167 to K-181; W-168 to E-182; L-169 to N-183; L-170 to K-184; S-171 to I-185; F-172 to L-186; K-173 to V-187; R-174 to K-188; G-175 to E-189; S-176 to T-190; A-177 to G-191; L-178 to Y-192; E-179 to F-193; E-180 to F-194; K-181 to I-195; E-182 to Y-196; N-183 to G-197; K-184 to Q-198; I-185 to V-199; L-186 to L-200; V-187 to Y-201; K-188 to T-202; E-189 to D-203; T-190 to K-204; G-191 to T-205; Y-192 to Y-206; F-193 to A-207; F-194 to M-208; I-195 to G-209; Y-196 to H-210; G-197 to L-211; Q-198 to I-212; V-199 to Q-213; L-200 to R-214; Y-201 to K-215; T-202 to K-216; D-203 to V-217; K-204 to H-218; T-205 to V-219; Y-206 to F-220; A-207 to G-221; M-208 to D-222; G-209 to E-223; H-210 to L-224; L-211 to S-225; I-212 to L-226; Q-213 to V-227; R-214 to T-228; K-215 to L-229; K-216 to F-230; V-217 to R-231; H-218 to C-232;

V-219 to I-233; F-220 to Q-234; G-221 to N-235; D-222 to M-236; E-223 to P-237; L-224 to E-238; S-225 to T-239; L-226 to L-240; V-227 to P-241; T-228 to N-242; L-229 to N-243; F-230 to S-244; R-231 to C-245; C-232 to Y-246; I-233 to S-247; Q-234 to A-248; N-235 to G-249; M-236 to I-250; P-237 to A-251; E-238 to K-252; T-239 to L-253; L-240 to E-254; P-241 to E-255; N-242 to G-256; N-243 to D-257; S-244 to E-258; C-245 to L-259; Y-246 to Q-260; S-247 to L-261; A-248 to A-262; G-249 to I-263; I-250 to P-264; A-251 to R-265; K-252 to E-266; L-253 to N-267; E-254 to A-268; E-255 to Q-269; G-256 to I-270; D-257 to S-271; E-258 to L-272; L-259 to D-273; Q-260 to G-274; L-261 to D-275; A-262 to V-276; I-263 to T-277; P-264 to F-278; R-265 to F-279; E-266 to G-280; N-267 to A-281; A-268 to L-282; Q-269 to K-283; I-270 to L-284; and S-271 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

[0154] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-

97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to G-142; S-129 to S-143; R-130 to Y-144; N-131 to T-145; K-132 to F-146; R-133 to V-147; A-134 to P-148; V-135 to W-149; Q-136 to L-150; G-137 to L-151; P-138 to S-152; E-139 to F-153; E-140 to K-154; T-141 to R-155; G-142 to G-156; S-143 to S-157; Y-144 to A-158; T-145 to L-159; F-146 to E-160; V-147 to E-161; P-148 to K-162; W-149 to E-163; L-150 to N-164; L-151 to K-165; S-152 to I-166; F-153 to L-167; K-154 to V-168; R-155 to K-169; G-156 to E-170; S-157 to T-171; A-158 to G-172; L-159 to Y-173; E-160 to F-174; E-161 to F-175; K-162 to I-176; E-163 to Y-177; N-164 to G-178; K-165 to Q-179; I-166 to V-180; L-167 to L-181; V-168 to Y-182; K-169 to T-183; E-170 to D-184; T-171 to K-185; G-172 to T-186; Y-173 to Y-187; F-174 to A-188; F-175 to M-189; I-176 to G-190; Y-177 to H-191; G-178 to L-192; Q-179 to I-193; V-180 to Q-194; L-181 to R-195; Y-182 to K-196; T-183 to K-197; D-184 to V-198; K-185 to H-199; T-186 to V-200; Y-187 to F-201; A-188 to G-202; M-189 to D-203; G-190 to E-204; H-191 to L-205; L-192 to S-206; I-193 to L-207; Q-194 to V-208; R-195 to T-209; K-196 to L-210; K-197 to F-211; V-198 to R-212; H-199 to C-213; V-200 to I-214; F-201 to Q-215; G-202 to N-216; D-203 to M-217; E-204 to P-218; L-205 to E-219; S-206 to T-220; L-207 to L-221; V-208 to P-222; T-209 to N-223; L-210 to N-224; F-211 to S-225; R-212 to C-226; C-213 to Y-227; I-214 to S-228; Q-215 to A-229; N-216 to G-230; M-217 to I-231; P-218 to A-232; E-219 to K-233; T-220 to L-234; L-221 to E-235; P-222 to E-236; N-223 to G-237; N-224 to D-238; S-225 to E-239; C-226 to L-240; Y-227 to Q-241; S-228 to L-242; A-229 to A-243; G-230 to I-244; I-231 to P-245; A-232 to R-246; K-233 to E-247; L-234 to N-248; E-235 to A-249; E-236 to Q-250; G-237 to I-251; D-238 to S-252; E-239 to L-253; L-240 to D-254; Q-241 to G-255; L-242 to D-256; A-243 to V-257; I-244 to T-258; P-245 to F-259; R-246 to F-260; E-247 to G-261; N-248 to A-262; A-249 to L-263; Q-250 to K-264; I-251 to L-265; and S-252 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%,

96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0155] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to F-15; D-2 to C-16; E-3 to S-17; S-4 to E-18; A-5 to K-19; K-6 to G-20; T-7 to E-21; L-8 to D-22; P-9 to M-23; P-10 to K-24; P-11 to V-25; C-12 to G-26; L-13 to Y-27; C-14 to D-28; F-15 to P-29; C-16 to I-30; S-17 to T-31; E-18 to P-32; K-19 to Q-33; G-20 to K-34; E-21 to E-35; D-22 to E-36; M-23 to G-37; K-24 to A-38; V-25 to W-39; G-26 to F-40; Y-27 to G-41; D-28 to I-42; P-29 to C-43; I-30 to R-44; T-31 to D-45; P-32 to G-46; Q-33 to R-47; K-34 to L-48; E-35 to L-49; E-36 to A-50; G-37 to A-51; A-38 to T-52; W-39 to L-53; F-40 to L-54; G-41 to L-55; I-42 to A-56; C-43 to L-57; R-44 to L-58; D-45 to S-59; G-46 to S-60; R-47 to S-61; L-48 to F-62; L-49 to T-63; A-50 to A-64; A-51 to M-65; T-52 to S-66; L-53 to L-67; L-54 to Y-68; L-55 to Q-69; A-56 to L-70; L-57 to A-71; L-58 to A-72; S-59 to L-73; S-60 to Q-74; S-61 to A-75; F-62 to D-76; T-63 to L-77; A-64 to M-78; M-65 to N-79; S-66 to L-80; L-67 to R-81; Y-68 to M-82; Q-69 to E-83; L-70 to L-84; A-71 to Q-85; A-72 to S-86; L-73 to Y-87; Q-74 to R-88; A-75 to G-89; D-76 to S-90; L-77 to A-91; M-78 to T-92; N-79 to P-93; L-80 to A-94; R-81 to A-95; M-82 to A-96; E-83 to G-97; L-84 to A-98; Q-85 to P-99; S-86 to E-100; Y-87 to L-101; R-88 to T-102; G-89 to A-103; S-90 to G-104; A-91 to V-105; T-92 to K-106; P-93 to L-107; A-94 to L-108; A-95 to T-109; A-96 to P-110; G-97 to A-111; A-98 to A-112; P-99 to P-113; E-100 to R-114; L-101 to P-115; T-102 to H-116; A-103 to N-117; G-104 to S-118; V-105 to S-119; K-106 to R-120; L-107 to G-121; L-108 to H-122; T-109 to R-123; P-110 to N-124; A-111 to R-125; A-112 to R-126; P-113 to A-127; R-114 to F-128; P-115 to Q-129; H-116 to G-130; N-117 to P-131; S-118 to E-132; S-119 to E-133; R-120 to T-134; G-121 to E-135; H-122 to Q-136; R-123 to D-137; N-124 to V-138; R-125 to D-139; R-126 to L-140; A-127 to S-141; F-128 to A-142; Q-129 to P-143; G-130 to P-144; P-131 to A-145; E-132 to P-146; E-133 to C-147; T-134 to L-148; E-135 to P-149; Q-136 to G-150; D-137 to C-151; V-138 to R-152; D-139 to H-153; L-140 to S-154; S-141 to Q-155; A-142 to H-156; P-143 to D-157; P-144 to D-158; A-145 to N-159; P-146 to G-160; C-147 to M-161; L-148 to N-162; P-149 to L-163; G-150 to R-164; C-151 to N-165; R-152 to I-166; H-153 to I-167; S-154 to Q-168; Q-155 to D-169; H-156 to C-170; D-157 to L-171; D-158 to Q-172; N-159 to L-173; G-160 to I-

174; M-161 to A-175; N-162 to D-176; L-163 to S-177; R-164 to D-178; N-165 to T-179; I-166 to P-180; I-167 to A-181; Q-168 to L-182; D-169 to E-183; C-170 to E-184; L-171 to K-185; Q-172 to E-186; L-173 to N-187; I-174 to K-188; A-175 to I-189; D-176 to V-190; S-177 to V-191; D-178 to R-192; T-179 to Q-193; P-180 to T-194; A-181 to G-195; L-182 to Y-196; E-183 to F-197; E-184 to F-198; K-185 to I-199; E-186 to Y-200; N-187 to S-201; K-188 to Q-202; I-189 to V-203; V-190 to L-204; V-191 to Y-205; R-192 to T-206; Q-193 to D-207; T-194 to P-208; G-195 to I-209; Y-196 to F-210; F-197 to A-211; F-198 to M-212; I-199 to G-213; Y-200 to H-214; S-201 to V-215; Q-202 to I-216; V-203 to Q-217; L-204 to R-218; Y-205 to K-219; T-206 to K-220; D-207 to V-221; P-208 to H-222; I-209 to V-223; F-210 to F-224; A-211 to G-225; M-212 to D-226; G-213 to E-227; H-214 to L-228; V-215 to S-229; I-216 to L-230; Q-217 to V-231; R-218 to T-232; K-219 to L-233; K-220 to F-234; V-221 to R-235; H-222 to C-236; V-223 to I-237; F-224 to Q-238; G-225 to N-239; D-226 to M-240; E-227 to P-241; L-228 to K-242; S-229 to T-243; L-230 to L-244; V-231 to P-245; T-232 to N-246; L-233 to N-247; F-234 to S-248; R-235 to C-249; C-236 to Y-250; I-237 to S-251; Q-238 to A-252; N-239 to G-253; M-240 to I-254; P-241 to A-255; K-242 to R-256; T-243 to L-257; L-244 to E-258; P-245 to E-259; N-246 to G-260; N-247 to D-261; S-248 to E-262; C-249 to I-263; Y-250 to Q-264; S-251 to L-265; A-252 to A-266; G-253 to I-267; I-254 to P-268; A-255 to R-269; R-256 to E-270; L-257 to N-271; E-258 to A-272; E-259 to Q-273; G-260 to I-274; D-261 to S-275; E-262 to R-276; I-263 to N-277; Q-264 to G-278; L-265 to D-279; A-266 to D-280; I-267 to T-281; P-268 to F-282; R-269 to F-283; E-270 to G-284; N-271 to A-285; A-272 to L-286; Q-273 to K-287; I-274 to L-288; and S-275 to L-289 of SEQ ID NO:38. The present invention is also directed to antibodies that bind BLYS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLYS polypeptides described above.

[0156] It will be recognized by one of ordinary skill in the art that some amino acid sequences of the BLYS polypeptides can be varied without significant effect of the structure or function of the polypeptide. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the polypeptide which determine activity.

[0157] Thus, the invention further includes antibodies that bind variations of BLYS polypeptides which show BLYS polypeptide functional activity (e.g., biological activity) or which include regions of BLYS polypeptide such as the polypeptide fragments described herein. Such mutants include deletions, insertions, inversions, repeats, and type substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main approaches for studying the tolerance of an amino acid sequence to change. The first method relies on the process of evolution, in which mutations are either accepted or rejected by natural selection. The second approach uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene and selections or screens to identify sequences that maintain functionality.

[0158] As the authors state, these studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at a certain position of the protein. For example, most buried amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Other such phenotypically silent substitutions are described in Bowie, J. U. et al., *supra*, and the references cited therein. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

[0159] Thus, antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3228, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to

increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence.

[0160] Antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3229, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as, a soluble biologically active fragment of another TNF ligand family member (e.g., CD40 Ligand), an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

[0161] Thus, the antibodies of the invention may bind BLyS polypeptides that include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 13).

TABLE 13. Conservative Amino Acid Substitutions.

Aromatic	Phenylalanine Tryptophan Tyrosine
Hydrophobic	Leucine Isoleucine Valine
Polar	Glutamine Asparagine
Basic	Arginine Lysine Histidine
Acidic	Aspartic Acid Glutamic Acid
Small	Alanine Serine Threonine Methionine Glycine

[0162] In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLYS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, even more preferably, not more than 40 conservative amino acid substitutions, still more preferably, not more than 30 conservative amino acid substitutions, and still even more preferably, not more than 20 conservative amino acid substitutions. In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLYS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

[0163] For example, site directed changes at the amino acid level of BLYS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLYS amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3228 including: M1 replaced

with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G,

I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; V142 replaced with A, G, I, L, S, T, or M; T143 replaced with A, G, I, L, S, M, or V; Q144 replaced with N; D145 replaced with E; L147 replaced with A, G, I, S, T, M, or V; Q148 replaced with N; L149 replaced with A, G, I, S, T, M, or V; I150 replaced with A, G, L, S, T, M, or V; A151 replaced with G, I, L, S, T, M, or V; D152 replaced with E; S153 replaced with A, G, I, L, T, M, or V; E154 replaced with D; T155 replaced with A, G, I, L, S, M, or V; T157 replaced with A, G, I, L, S, M, or V; I158 replaced with A, G, L, S, T, M, or V; Q159 replaced with N; K160 replaced with H, or R; G161 replaced with A, I, L, S, T, M, or V; S162 replaced with A, G, I, L, T, M, or V; Y163 replaced with F, or W; T164 replaced with A, G, I, L, S, M, or V; F165 replaced with W, or Y; V166 replaced with A, G, I, L, S, T, or M; W168 replaced with F, or Y; L169 replaced with A, G, I, S, T, M, or V; L170 replaced with A, G, I, S, T, M, or V; S171 replaced with A, G, I, L, T, M, or V; F172 replaced with W, or Y; K173 replaced with H, or R; R174 replaced with H, or K; G175 replaced with A, I, L, S, T, M, or V; S176 replaced with A, G, I, L, T, M, or V; A177 replaced with G, I, L, S, T, M, or

V; L178 replaced with A, G, I, S, T, M, or V; E179 replaced with D; E180 replaced with D; K181 replaced with H, or R; E182 replaced with D; N183 replaced with Q; K184 replaced with H, or R; I185 replaced with A, G, L, S, T, M, or V; L186 replaced with A, G, I, S, T, M, or V; V187 replaced with A, G, I, L, S, T, or M; K188 replaced with H, or R; E189 replaced with D; T190 replaced with A, G, I, L, S, M, or V; G191 replaced with A, I, L, S, T, M, or V; Y192 replaced with F, or W; F193 replaced with W, or Y; F194 replaced with W, or Y; I195 replaced with A, G, L, S, T, M, or V; Y196 replaced with F, or W; G197 replaced with A, I, L, S, T, M, or V; Q198 replaced with N; V199 replaced with A, G, I, L, S, T, or M; L200 replaced with A, G, I, S, T, M, or V; Y201 replaced with F, or W; T202 replaced with A, G, I, L, S, M, or V; D203 replaced with E; K204 replaced with H, or R; T205 replaced with A, G, I, L, S, M, or V; Y206 replaced with F, or W; A207 replaced with G, I, L, S, T, M, or V; M208 replaced with A, G, I, L, S, T, or V; G209 replaced with A, I, L, S, T, M, or V; H210 replaced with K, or R; L211 replaced with A, G, I, S, T, M, or V; I212 replaced with A, G, L, S, T, M, or V; Q213 replaced with N; R214 replaced with H, or K; K215 replaced with H, or R; K216 replaced with H, or R; V217 replaced with A, G, I, L, S, T, or M; H218 replaced with K, or R; V219 replaced with A, G, I, L, S, T, or M; F220 replaced with W, or Y; G221 replaced with A, I, L, S, T, M, or V; D222 replaced with E; E223 replaced with D; L224 replaced with A, G, I, S, T, M, or V; S225 replaced with A, G, I, L, T, M, or V; L226 replaced with A, G, I, S, T, M, or V; V227 replaced with A, G, I, L, S, T, or M; T228 replaced with A, G, I, L, S, M, or V; L229 replaced with A, G, I, S, T, M, or V; F230 replaced with W, or Y; R231 replaced with H, or K; I233 replaced with A, G, L, S, T, M, or V; Q234 replaced with N; N235 replaced with Q; M236 replaced with A, G, I, L, S, T, or V; E238 replaced with D; T239 replaced with A, G, I, L, S, M, or V; L240 replaced with A, G, I, S, T, M, or V; N242 replaced with Q; N243 replaced with Q; S244 replaced with A, G, I, L, T, M, or V; Y246 replaced with F, or W; S247 replaced with A, G, I, L, T, M, or V; A248 replaced with G, I, L, S, T, M, or V; G249 replaced with A, I, L, S, T, M, or V; I250 replaced with A, G, L, S, T, M, or V; A251 replaced with G, I, L, S, T, M, or V; K252 replaced with H, or R; L253 replaced with A, G, I, S, T, M, or V; E254 replaced with D; E255 replaced with D; G256 replaced with A, I, L, S, T, M, or V; D257 replaced with E; E258 replaced with D; L259 replaced with A, G, I, S, T, M, or V; Q260 replaced with N; L261 replaced with A, G, I, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; I263 replaced with A, G, L,

S, T, M, or V; R265 replaced with H, or K; E266 replaced with D; N267 replaced with Q; A268 replaced with G, I, L, S, T, M, or V; Q269 replaced with N; I270 replaced with A, G, L, S, T, M, or V; S271 replaced with A, G, I, L, T, M, or V; L272 replaced with A, G, I, S, T, M, or V; D273 replaced with E; G274 replaced with A, I, L, S, T, M, or V; D275 replaced with E; V276 replaced with A, G, I, L, S, T, or M; T277 replaced with A, G, I, L, S, M, or V; F278 replaced with W, or Y; F279 replaced with W, or Y; G280 replaced with A, I, L, S, T, M, or V; A281 replaced with G, I, L, S, T, M, or V; L282 replaced with A, G, I, S, T, M, or V; K283 replaced with H, or R; L284 replaced with A, G, I, S, T, M, or V; and/or L285 replaced with A, G, I, S, T, M, or V.

[0164] In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3229 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55

replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; G142 replaced with A, I, L, S, T, M, or V;

S143 replaced with A, G, I, L, T, M, or V; Y144 replaced with F, or W; T145 replaced with A, G, I, L, S, M, or V; F146 replaced with W, or Y; V147 replaced with A, G, I, L, S, T, or M; W149 replaced with F, or Y; L150 replaced with A, G, I, S, T, M, or V; L151 replaced with A, G, I, S, T, M, or V; S152 replaced with A, G, I, L, T, M, or V; F153 replaced with W, or Y; K154 replaced with H, or R; R155 replaced with H, or K; G156 replaced with A, I, L, S, T, M, or V; S157 replaced with A, G, I, L, T, M, or V; A158 replaced with G, I, L, S, T, M, or V; L159 replaced with A, G, I, S, T, M, or V; E160 replaced with D; E161 replaced with D; K162 replaced with H, or R; E163 replaced with D; N164 replaced with Q; K165 replaced with H, or R; I166 replaced with A, G, L, S, T, M, or V; L167 replaced with A, G, I, S, T, M, or V; V168 replaced with A, G, I, L, S, T, or M; K169 replaced with H, or R; E170 replaced with D; T171 replaced with A, G, I, L, S, M, or V; G172 replaced with A, I, L, S, T, M, or V; Y173 replaced with F, or W; F174 replaced with W, or Y; F175 replaced with W, or Y; I176 replaced with A, G, L, S, T, M, or V; Y177 replaced with F, or W; G178 replaced with A, I, L, S, T, M, or V; Q179 replaced with N; V180 replaced with A, G, I, L, S, T, or M; L181 replaced with A, G, I, S, T, M, or V; Y182 replaced with F, or W; T183 replaced with A, G, I, L, S, M, or V; D184 replaced with E; K185 replaced with H, or R; T186 replaced with A, G, I, L, S, M, or V; Y187 replaced with F, or W; A188 replaced with G, I, L, S, T, M, or V; M189 replaced with A, G, I, L, S, T, or V; G190 replaced with A, I, L, S, T, M, or V; H191 replaced with K, or R; L192 replaced with A, G, I, S, T, M, or V; I193 replaced with A, G, L, S, T, M, or V; Q194 replaced with N; R195 replaced with H, or K; K196 replaced with H, or R; K197 replaced with H, or R; V198 replaced with A, G, I, L, S, T, or M; H199 replaced with K, or R; V200 replaced with A, G, I, L, S, T, or M; F201 replaced with W, or Y; G202 replaced with A, I, L, S, T, M, or V; D203 replaced with E; E204 replaced with D; L205 replaced with A, G, I, S, T, M, or V; S206 replaced with A, G, I, L, T, M, or V; L207 replaced with A, G, I, S, T, M, or V; V208 replaced with A, G, I, L, S, T, or M; T209 replaced with A, G, I, L, S, M, or V; L210 replaced with A, G, I, S, T, M, or V; F211 replaced with W, or Y; R212 replaced with H, or K; I214 replaced with A, G, L, S, T, M, or V; Q215 replaced with N; N216 replaced with Q; M217 replaced with A, G, I, L, S, T, or V; E219 replaced with D; T220 replaced with A, G, I, L, S, M, or V; L221 replaced with A, G, I, S, T, M, or V; N223 replaced with Q; N224 replaced with Q; S225 replaced with A, G, I, L, T, M, or V; Y227 replaced with F, or W; S228 replaced with A, G, I, L, T,

M, or V; A229 replaced with G, I, L, S, T, M, or V; G230 replaced with A, I, L, S, T, M, or V; I231 replaced with A, G, L, S, T, M, or V; A232 replaced with G, I, L, S, T, M, or V; K233 replaced with H, or R; L234 replaced with A, G, I, S, T, M, or V; E235 replaced with D; E236 replaced with D; G237 replaced with A, I, L, S, T, M, or V; D238 replaced with E; E239 replaced with D; L240 replaced with A, G, I, S, T, M, or V; Q241 replaced with N; L242 replaced with A, G, I, S, T, M, or V; A243 replaced with G, I, L, S, T, M, or V; I244 replaced with A, G, L, S, T, M, or V; R246 replaced with H, or K; E247 replaced with D; N248 replaced with Q; A249 replaced with G, I, L, S, T, M, or V; Q250 replaced with N; I251 replaced with A, G, L, S, T, M, or V; S252 replaced with A, G, I, L, T, M, or V; L253 replaced with A, G, I, S, T, M, or V; D254 replaced with E; G255 replaced with A, I, L, S, T, M, or V; D256 replaced with E; V257 replaced with A, G, I, L, S, T, or M; T258 replaced with A, G, I, L, S, M, or V; F259 replaced with W, or Y; F260 replaced with W, or Y; G261 replaced with A, I, L, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; L263 replaced with A, G, I, S, T, M, or V; K264 replaced with H, or R; L265 replaced with A, G, I, S, T, M, or V; and/or L266 replaced with A, G, I, S, T, M, or V.

[0165] In another embodiment, site directed changes at the amino acid level of BLYS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLYS amino acid sequences containing conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

[0166] Amino acids in the BLYS polypeptides that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for functional activity, such ligand binding and the ability to stimulate lymphocyte (e.g., B cell) as, for example, proliferation, differentiation, and/or activation. Accordingly, antibodies of the present invention may bind amino acids in the BLYS polypeptides that are essential for function. In preferred embodiments, antibodies of the present invention bind amino acids in the BLYS polypeptides that are essential for function and inhibit BLYS polypeptide function. In other preferred embodiments, antibodies of the present invention bind amino acids in the BLYS polypeptides that are essential for function and enhance BLYS polypeptide function.

[0167] Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutical formulations, because aggregates can be immunogenic (Pinckard *et al.*, *Clin. Exp. Immunol.* 2:331-340 (1967); Robbins *et al.*, *Diabetes* 36: 838-845 (1987); Cleland *et al.*, *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993).

[0168] In another embodiment, the invention provides for antibodies that bind polypeptides having amino acid sequences containing non-conservative substitutions of the amino acid sequence provided in SEQ ID NO:3228. For example, non-conservative substitutions of the BLYS protein sequence provided in SEQ ID NO:3228 include: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H,

K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P,

or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A93 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G94 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A107 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F115 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q,

F, W, Y, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q144 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D145 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C146 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L149 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D152 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S153 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E154 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T155 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P156 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q159 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K160 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G161

replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S162 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y163 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T164 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F165 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P167 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W168 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L169 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L170 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F172 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K173 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R174 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G175 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A177 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E179 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E180 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K181 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E182 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N183 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K184 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I185 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L186 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V187 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K188 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E189 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G191 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y192 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F193 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F194 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I195 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y196 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G197 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q198 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V199 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K204 replaced with D, E, A, G, I, L,

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